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THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF
THE NATIONAL TUBERCULOSIS ASSOCIATION

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VOLUME XXXVI
JULY-DECEMBER, 1937

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

10667

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THE CLINIC, THE LABORATORY AND THE FIELD

The Address of the President[1]

ESMOND R. LONG[2]

Uniquely in the control of human disease the campaign against tuberculosis combines the three powerful forces of medical skill, exact study by technical device, and a far flung organization for reaching the mass of people and bestowing the benefits of modern science.

These forces, or rather their domain, may briefly be designated the clinic, the laboratory and the field. And in this short list is comprehended not only the modern attack on the disease, but in remarkable chronological succession the whole history of tuberculosis.

So logical does this combination of forces seem to us to-day, allied as we are in the antituberculosis campaign, and so effective does it appear to our close-range view, that it is difficult to imagine a successful war upon this disease without it. But in the long course of medical history the one has slowly waited for another, and it is only fifty years since the tremendous power of the third was added to the spectacular yet less effective advance of the first two.

In no ailment has the cultivation of what we may call the field been as important as in tuberculosis. Medical history furnishes many examples of quick control of disease through the combined operation of the clinic and the laboratory. In smallpox and diphtheria after centuries of clinical understanding the laboratory furnished a rapid short cut to mastery. The public required persuasion, to be sure, before preventive methods became general, but no such elaborate organization needed to be built as has been the case with tuberculosis. Neither the laboratory nor the clinic has furnished a short cut to its control. In the extraordinary check of typhoid fever, once a wide spread scourge and now a rarity, the laboratory, coming to the aid of the clinic, furnished a ready basis for effective sanitary engineering, while the bulk of the population remained ignorant of the measures taken for their protection. The

[1] Delivered at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 31, 1937.

[2] The Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

water that spreads typhoid fever is subject to mechanical supervision; the air through which tuberculosis is spread unfortunately is not. Other comparisons might be made, but it is enough to say that the control of tuberculosis through intensive cultivation of the field is without parallel in the attack upon sickness.

Medical familiarity with tuberculosis is almost as old as any medical writing. The clinical descriptions of the Hippocratic school of physicians leave no doubt of the character of the disease in ancient times. The illness was clearly set apart, on the basis of symptoms, as a clinical entity, and treated according to the best thought of the time. But how common it was, how important in the total list of diseases, there is no direct report to show. By an indirect approach we can make some guess, as we know something of the manner of living, the degree of crowding, the amount of malnutrition and other environmental factors in the life of ancient peoples. Some hint of a demographic outlook, some consciousness, so to speak, of the field, is to be seen in ancient correlation with varying climatic states, but the field was practically uncultivated, and was to stay so for many centuries.

Clinical practice remained the sole element in the conscious fight against tuberculosis until the laboratory science of pathology brought fresh understanding. This lengthy period from the time when the well-known symptoms of advanced illness first made the diagnosis until the day when experience at the necropsy table gave the disease a new definition has been aptly termed the period "from consumption to tuberculosis."

After the seventeenth century the clinic and the laboratory were allied. It is true, the laboratory science of tuberculosis had its vague beginnings long before this, even in Hippocrates's own time, when significant characteristics of the sputum of consumptives were recorded. But the deliberate opening of the human body, the painstaking objective study, and final identification of symptoms and organic visceral change, by the seventeenth century anatomists, were the first great strides, and perhaps the greatest steps, in the understanding of tuberculosis.

Yet it cannot be said that this laboratory contribution to the knowledge of the clinic had any immediate effect on the control of tuberculosis. To be sure it brought the disease out of the dark into the open of new investigation, but no physician of the time of Sylvius and Morton could attack tuberculosis the better because he knew his patients' symptoms came from cheesy degeneration of the lungs. Not that the new dis-

covery had no effect on medical practice. Sylvius himself promptly incorporated his anatomical findings in his philosophical concept of the disorder, and treated the latter accordingly, but the concept was wrong, and the treatment presumably worthless also. For the rank and file in medical practice the therapy of tuberculosis was empiric, as it is to large extent to-day, and the horseback riding of Sydenham was as effective a mode of treatment as any of the supposedly refined procedures based on anatomical understanding.

But whether the combination was at once effective in the clinic or not, the clinic and the laboratory were fused for all the future. The long chain of technical investigation that was to lead from the identification of the multitude of forms of tuberculosis to recognition of its specific cause and to perfected means of diagnosis was begun. The great advances in tuberculosis from the end of the seventeenth to the beginning of the nineteenth century were in the laboratory. For a century laboratory progress was to be confined to the gathering experience at the necropsy table. Out of the opening of thousands of bodies, culminating in the brilliant synthesis of knowledge by Laennec, came understanding of the whole anatomical course of tuberculosis from the smallest tubercle to fatal cavities and pneumonic consolidation of the lungs. In the identification of phthisis and scrofula the laboratory had vastly widened the field of tuberculosis, for scrofula for a thousand years had been almost the commonest serious ailment of mankind, and phthisis was carrying off one-fifth of the population. The laboratory made it apparent that tuberculosis was the most widespread of all chronic diseases, and it could be truly said then, as was said later, that "everyone has a little tuberculosis."

At the opening of the nineteenth century the tuberculosis clinic was rejuvenated by epoch-marking developments in diagnosis. Just as the period of greatest anatomical progress was closing, a period of extraordinary clinical advance was beginning. And remarkably, Laennec, who had so much to do with settling anatomical dispute, had a major part in the new development. If the century before Laennec was the century of impressive pathological unfolding, the century following was one of notable increase in knowledge through the art of physical diagnosis. Delicate touch and listening opened a new world to the clinician, who for centuries had stood helpless, waiting for unmistakable symptoms to develop. With physical diagnosis, for the first time, came the early case.

In the middle of the nineteenth century dramatic developments, wholly unrelated, occurred in both the clinic and the laboratory of tuberculosis. The clinical innovation was the sanatorium. Coming at the close of the exercise period in the treatment of tuberculosis, and itself devised originally as a school for exercise, the sanatorium later developed into exactly the opposite, a place for recovery through rest. For some decades it was an uncomplicated clinical experiment. The early sanatoria had no laboratories, as there was nothing to investigate, except the body after death, and there was no attempt to reach the masses. As late as 1908 Osler wrote, "At present we are in the sanatorium phase of treatment. . . . But the disease is so widely prevalent that we can never hope to place sanatorium treatment at the disposal of more than a very small percentage of patients." And yet in less than twenty years health officers engaged in the control of tuberculosis had come to accept a requirement of one sanatorium bed per annual death from tuberculosis in any community as the minimum standard for adequate control of the disease. Within a few years, experienced men in the field had set two beds per annual death as a better goal. In 1908 only 12,000 sanatorium beds were available for tuberculous patients, but in 1928 the number was nearly 70,000.

In those two decades sanatoria, springing up throughout the country, had proved effective demonstration centres, and an awakened sense of public health responsibility was rapidly making them available not to the fortunate few, but to the population at large. The sanatorium had reached the field. To-day there are 95,000 beds for the treatment of tuberculosis in the United States.

Coincident, as I have said, with the first operation of sanatoria, came two laboratory advances in the understanding of tuberculosis, both of them to be of the utmost practical importance. The first was a simple extension from the gross to the minute anatomy of tuberculosis. The microscope and the microtome, and soon the development of tissue stains, greatly refined the understanding of tuberculosis, which had begun two centuries before when coarse cheesy tubercles were first recognized as distinctive. The Cellular Pathology was giving new breath of life to all medicine, and the science of tuberculosis had its full share of advance with the new knowledge and technique.

The other development was the demonstration that tuberculosis is an infectious disease. The early inoculation experience proving its transmissibility was followed by Koch's actual demonstration of the cause.

The laboratory had become "practical" at last, for here was a development which, it would seem, the clinic could not afford to ignore. Strangely enough, it did ignore it for a time, probably because the laboratory itself had proved tuberculosis so nearly universal, and inevitable, that the recognition of its cause seemed at first of more academic than practical significance.

But measured against the whole history of tuberculosis the lag between the discovery of the tubercle bacillus and the application of the discovery in preventive medicine was infinitesimal. Indeed but a few years later, just fifty years ago, to be exact, the rational application of all facts at hand began.

Up to this time, although tuberculosis had long been decreasing through the operation of certain social causes, medical science could not claim, either through the clinic or the laboratory, much share in mass control of the disease. With the advent of the public health movement the share of medicine in the conquest became unmistakable.

In 1887 Sir Robert Philip established in Edinburgh the original dispensary for attack upon tuberculosis. This was soon followed, in New York City, by the first attempt at comprehensive public health control of the disease. And from these two beginnings has grown a far reaching campaign that today seems to follow the only logical course. The dispensary was the precursor of the present elaborate system of ambulant treatment, field nursing, case finding and provision for care of patients discovered, a system that has brought into antituberculosis work not only the clinician, not only the laboratory investigator and technician, but all the forces of public health, including a trained nursing and social service personnel and a vast army of lay workers who have succeeded in popularizing the subject and greatly facilitated the work of the technically trained forces.

Two thousand years of the clinic, three hundred of the laboratory and fifty years of this intensive cultivation of the field! To the first two we may credit the understanding of tuberculosis, but to the last we may indeed look for its ultimate practical eradication.

We are now, after long years, at a point where the three effective forces in the campaign are advancing simultaneously, and dependent on each other. If it is true that the field could make no progress whatsoever without the clinic and the laboratory, it is equally a fact that the clinic and laboratory without the field forces would only dent the mass problem, as they did in the past. Within recent decades the laboratory has

provided the clinic with the X-ray and the tuberculin test, but without the case-finding organization effected by the field personnel these two powerful weapons in the antituberculosis campaign would have a relatively restricted application. Within recent years, too, the clinic has introduced new and unusually successful methods for the treatment of tuberculosis, but, without the extensive dispensary, hospital and sanatorium facilities brought into existence through a well calculated propagandizing of the field, the benefits of this treatment would reach but a few of the enormous numbers favored at present.

In America this effective combination has resulted from thirty years work by the National Tuberculosis Association. The development of a wise unified plan is evident in the long series of annual meetings of the Association, each with its scientific sessions, representing the clinic and the laboratory, and its sessions for social work and administration, representing the field. The more recent system of combined section meetings testifies to a growing appreciation of the fact that these are not separate departments in the antituberculosis campaign, but a collection of vital interests to be cultivated together.

No one of these forces can afford to stand still. Each has the job of technical application of present understanding, but for each there is a road forward. We are essentially a research organization. For the clinic the history of tuberculosis is a long story of changing therapy. There is no reason to suppose that we have at last reached the top. Collapse therapy is the triumph of the moment, but we are too close to recent developments to know whether it is the solution or a simple phase of advancement in treatment of the disease. Continued investigation is essential. The laboratory in tuberculosis must keep pace with general scientific advance, and need not be deterred by any criticism of impracticality. Use will always be found for what is proved to be true. The first laboratory advance, anatomical understanding, probably in the beginning seemed of mere theoretical interest to the clinic, but to-day's indispensable X-ray film would be meaningless without the laboratory-built understanding of the lesions for which the shadows stand.

For the field remains the hardest task of all. Its work will continue to be the development of machinery for finding the cases of tuberculosis, and by education, legislation and otherwise to make sure of their adequate care and thereby prevent spread of the disease. This is difficult enough, but a further concern lies in the fact that our mass methods have outmoded some of the old established methods of individual medical

practice. The field operation of antituberculosis measures, essential, as we have seen, to mass control of the disease, has pioneered in new procedures in preventive medicine. We are at a point where leadership in administration and social planning must pioneer further to fit the new harmoniously to the old. In all probability at some future time—and it may be decades hence—the law of diminishing returns will operate so that the need for an elaborate voluntary organization to check tuberculosis will be past. Presumably, however, there will always be a residuum of tuberculosis, just as there is of typhoid fever and other nearly conquered diseases. The prevention of spread from this residuum must be recognized as a continuing public health problem of importance. The ensurance of an effective, permanent official program to keep this residuum at minimal proportions, is, as conceived by the Founders, the final responsibility of our field organization.

ULCERATIVE TUBERCULOUS TRACHEOBRONCHITIS[1]

JOHN B. BARNWELL, JOHN LITTIG AND JOHN E. CULP

INTRODUCTION

In spite of a definite symptom complex, tuberculosis of the airway below the larynx has only recently been recognized by the clinician. Like laryngeal tuberculosis, it adds gravity to the prognosis; yet it shares in none of the benefits of modern collapse therapy. Two factors are chiefly responsible for having kept obscure this serious complication of pulmonary tuberculosis. First, it is inaccessible to the usual methods of examination; and second, the routine necropsy technique of examining the thoracic viscera is not directed toward the detection of its frequency.

Clinical contributions to the literature are all of recent date. Various types of obstructive lesions of the trachea, main and lobar bronchi, occurring as a complication in pulmonary tuberculosis, are reported. The following are the main contributions in the American literature.

Schonwald (1), Clerf (2), McConkey (3), Myerson (6), Tucker (7), Eloesser (8) and Coryllos (9) have recognized and described bronchial complications under the following headings: (1) ulcerative lesions, (2) stenosing fibrotic lesions, (3) caseous thrombus, (4) fibrinous plug, (5) tuberculoma and (6) tuberculous granulation tissue; all causing various degrees of stenosis and obstruction, and giving rise to definite clinical signs and symptoms. Lord (10), Hoover (11), McPhedran (12), and Norris and Landis (13) have referred to tuberculosis of the trachea and bronchi, and Jackson (14) has described its endoscopic appearance. Eloesser, in addition, describes extramural lesions and a diffuse stenosis of the smaller bronchi (obliterative bronchiolitis).

In the broad group of tracheal and bronchial complications represented in the literature, there are two common features: (1) tuberculous aetiology and (2) tracheal or bronchial obstruction. In our experience, no generalization could be made if all the cases presenting these two common features were grouped under one head. The one subgroup which most nearly fitted into or could be classified as a clinical entity were

[1] From the Department of Internal Medicine, Medical School, University of Michigan, Ann Arbor, Michigan.

those with ulcerations. These cases with ulcerations frequently have features in common with other groups, namely, extrinsic pressure, cicatricial stenosis and tuberculoma. For clarification of both the diagnosis and the clinical picture, we have chosen to present at this time only those with tuberculous ulcerations.

Our interest in this complication was aroused by our observation of several patients whose symptoms were unexplained until the bronchoscopist found tuberculous ulcers of the mucosa of the trachea and bronchi. Since this observation in 1929, awareness of the possibility has led to an antemortem clinical diagnosis in nine cases of tuberculous ulcerations of these structures. These observations have stimulated autopsy studies to be reported elsewhere, (Bugher, Littig and Culp (16)).

We have selected for this report six typical cases of ulcerative tuberculous tracheobronchitis seen at the University of Michigan Hospital in the past seven years, all of which were recognized by the clinician first, and later the clinical diagnosis was verified by the bronchoscopist. Other cases with a clinical diagnosis, but in which no bronchoscopy was obtained, are not included in this report.

CASE HISTORIES

1: No. 205796, M. P., white, woman, age 29, was admitted November 6, 1928, with a history suggesting a catarrhal onset of pulmonary tuberculosis extending over a four-year period. The history was unusual only because of definite shortness of breath on moderate exertion. Examination of the chest at this time revealed impaired resonance over the upper third of the right lung, and transient râles over the left, localized beneath the left clavicle. The sputum contained tubercle bacilli, and the admission X-ray examination, dated November 6, 1928, (figure 1A) showed soft blotchy shadows in the upper left lung field, suggestive of tuberculosis. A dense triangular shadow was interpreted as representing atelectasis of the right upper lobe. This shadow of atelectasis was not present in a film taken in August, 1928, three months before admission, but in its place was the moderately advanced mottling of this lobe.

Ten weeks later, January 21, 1929, the dense shadow on the right had again been replaced by the picture of August, 1928. The clinical course was considered satisfactory, cough less, sputum markedly decreased, and a gain of nine pounds in weight. In June, 1929, the patient had an attack, characterized by a severe paroxysm of coughing, dyspnoea, and cyanosis. At this time a rough expiratory sound was audible thoroughout both lung fields. X-rays of May 10 and June 27, 1929, showed no change other than slight increase of the shadows in the upper left lung.

Fig. 1A

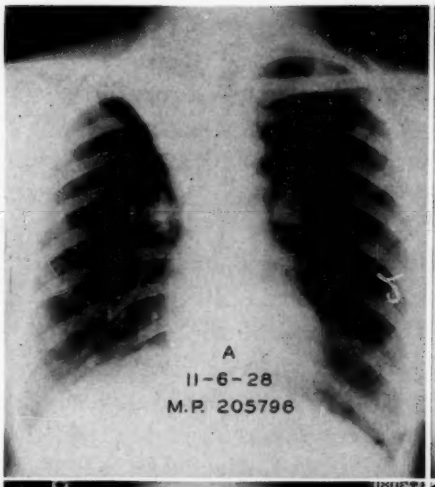


Fig. 1B

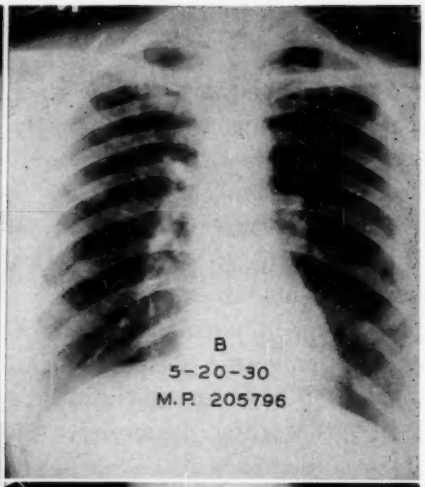


Fig. 1C

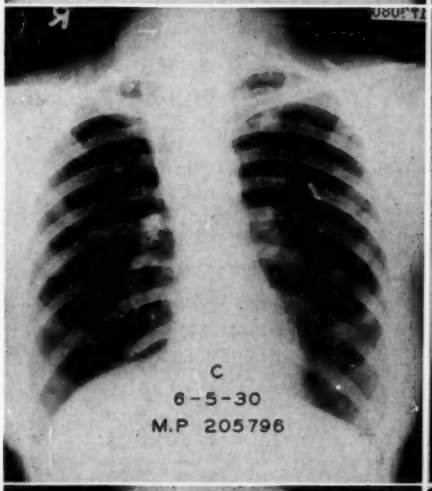


Fig. 1D

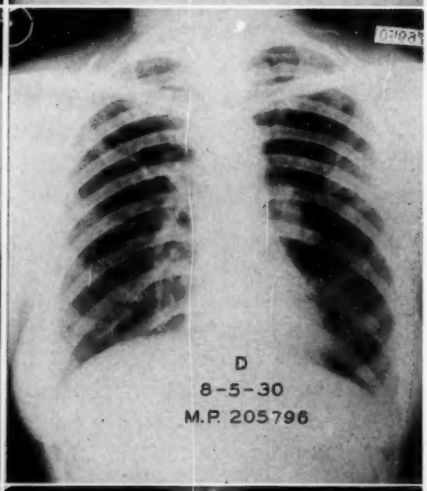


Fig. 1E

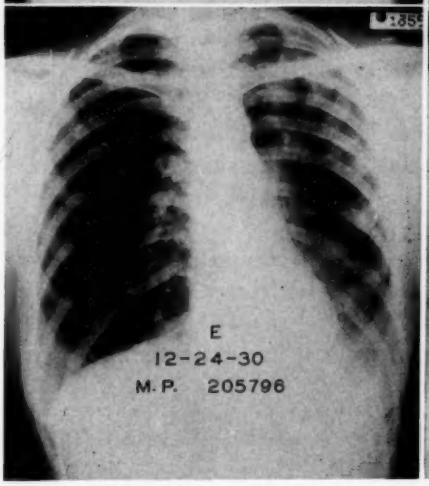
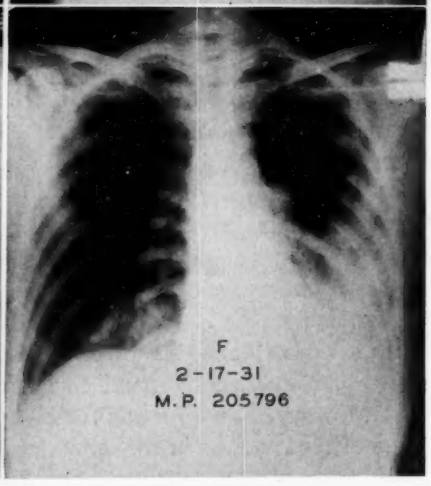


Fig. 1F



In August, 1929, atelectasis was still absent and slight clearing was noted in both lung fields. However, the shadow of atelectasis reappeared in the film of November 5, 1929, and persisted in the X-ray of January 20, 1930, but appeared smaller on each examination. The shadow representing atelectasis was again absent from the X-rays of March 7, March 11, and May 20, 1930, (figure 1B) but reappeared smaller than ever in the film of June 5, 1930, (figure 1C) at which time there was an increase of shadows in the third left anterior interspace. A comparison of figure 1A with figure 1C represents the very slight increase of shadow developing in nineteen months of conservative treatment, six months on a Bradford frame for suspected Pott's disease, the remainder at complete bedrest.

During the last twelve months of this period, the patient continued to experience periodic "asthma-like" attacks, variable in frequency and severity,

Case 1

Fig. 1A. Atelectasis of right upper lobe on admission with no shift of trachea, mediastinum or diaphragm.

Fig. 1B. Right upper lobe inflated. Note the mottling in the right first anterior interspace.

Fig. 1C. The result of nineteen months bed-rest. The right upper lobe is again atelectatic after repeated reëxpansion, and is now shrunken. The mottling seen in the right first anterior interspace in B, taken 16 days before, has now disappeared into the atelectatic upper lobe. In spite of the small size of this lobe there is no displacement of the trachea or mediastinum or elevation of the diaphragm. The slight increase of shadow in the left midlung field represents the only change from the condition seen in A.

Fig. 1D. Six weeks following bronchoscopy and biopsy. Mottled right upper lobe again expanded. Beginning of rapid increases in the left lung.

Fig. 1E. Four months continued progression in the left lung.

Fig. 1F. Twelve days after the second bronchoscopy, six weeks before death. Beginning involvement right base and further extension on the left. This shadow at the left base suggests atelectasis, but by the time of autopsy there was tuberculous pneumonia in this area.

associated with paroxysms of coughing. The attacks were very alarming and the respiratory distress tremendous; they were separated by periods of apparent well-being, except for occasional rises in temperature to 101°F. Rhonchi were palpable over both lungs; hoarseness had become a symptom; an ulcer was present in the larynx (November 25, 1929).

June 19, 1930, the patient was bronchoscoped, (Dr. Furstenberg) the right bronchus being grossly ulcerated four centimeters below the carina. Large masses of granulation tissue extended from the ulcerated area into the bronchial lumen. A biopsy was taken from the ulcerated area and reported as caseous tuberculosis.

It may be noted that up to this time the atelectasis appeared and disappeared at intervals. X-rays, frequently interspersed with fluoroscopic observations, failed to determine any definite relation between the appearance of the atelectasis and the occurrence of symptoms. Although no observations

were made during an acute attack, it may be said that the atelectasis was both present and absent during periods of comparative comfort. When the shadow was present, all of the previous mottling disappeared, indicating that the involvement was principally confined to the lobe which became atelectatic. August 5, 1930, the X-ray (figure 1D) showed the final disappearance of the atelectasis and the beginning of rapid increases in shadows in the left lung, which continued through the X-rays of October 23, 1930, and December 24, 1930 (figure 1E).

February 5, 1931, a second bronchoscopy was done (Mr. Nelson); the lumen of the trachea was reported reduced, and the mucosa appeared oedematous; no tracheal rings could be seen. The mucosa of both main bronchi was in a similar state, with narrowing of the lumen, but without ulceration.

The symptoms were greatly aggravated following this procedure, a low tracheotomy was performed (Dr. Alexander), suction was established; but without definitely influencing the patient's condition. Twelve days after the second bronchoscopy, an X-ray of the chest dated February 17, 1931 (figure 1F) revealed a continuation of increases on the left and the beginning of massive changes on the right, both of which were continued in the X-rays of April 1, 1931, taken three days before death. Attention is called to the marked and rapid increase in X-ray shadows following the first bronchoscopy, at which time a biopsy was taken, (figure 1C before bronchoscopy), and (figures 1D & 1E after bronchoscopy), and exaggerated after the second bronchoscopy (figure 1F). This is especially noteworthy when viewed in the light of the twenty months preceding bronchoscopy, when little parenchymal change was observed (figures 1A & 1C).

Death followed six years and seven months after the onset of tuberculosis, twenty-two months after the first attack of dyspnoea, twenty-nine months after the beginning of conservative treatment, ten months after the first bronchoscopy and two months after the second bronchoscopy.

Autopsy (Dr. Weller): The right upper lobe which had been the site of intermittent atelectases, but which had been reëxpanded for eight months before death, was grayish in color and emphysematous in appearance. On cut section, it showed emphysema and occasional small healed tubercles. The bronchus to this lobe was apparently constricted by enlarged glands surrounding the bifurcation of the trachea. The bronchi were generally filled with purulent material, but chiefly on the left. The mucosa was swollen, but no ulcer was seen. The right lower lobe and the two left lobes contained areas of caseous pneumonia, beginning cavitation and atelectasis.

2: No. 174084, T. S., white, woman, age 43 years, was admitted July 1, 1927, with complaints of weakness and "wheezing in the upper left lung." Aside from slight cough, afternoon fever, and the presence of tuberculous infection

in her family, her history was noncontributory. Coarse râles were audible in the upper left anterior lung. The tuberculin test was positive, but the sputum contained no tubercle bacilli. X-rays in July, August and October, 1927, showed a shadow off the left border of the heart that was not diagnostic of tuberculosis but that increased in size in three months' observation.

The two year course at home finally ended in admission to the Michigan State Sanatorium. There the sputum contained tubercle bacilli and there was a daily febrile reaction. The sanatorium admission X-ray, July 31, 1929 (figure 2A)[2], showed a slight decrease in the shadow off the left border of the heart since October, 1927. The next X-ray, December 4, 1929 (figure 2B), showed the trachea, mediastinum and heart retracted to the left and a homogenous shadow occupying the left base up to the third anterior rib. This shadow is now interpreted as atelectasis, but then as pneumonia. The left lung was collapsed by pneumothorax induced February 15, 1930, and an X-ray two days later showed some aeration in the previously atelectatic left lower lobe, but atelectasis now of the left upper lobe though the total collapse was no more than 20 per cent. The next X-ray, April 3, 1930 (figure 2C), shows atelectasis of the left lung and the beginning contraction of this lung which progressed to the degree seen on October 4, 1932 (figure 2D). This progressive contraction of the left lung was little influenced by paralysis of the left diaphragm, May 30, 1930, and cauterization of several adhesions, January 17, 1931 (Dr. Alexander). Both operations were indicated by the continued presence of tubercle bacilli in the sputum in spite of the degree of collapse already achieved.

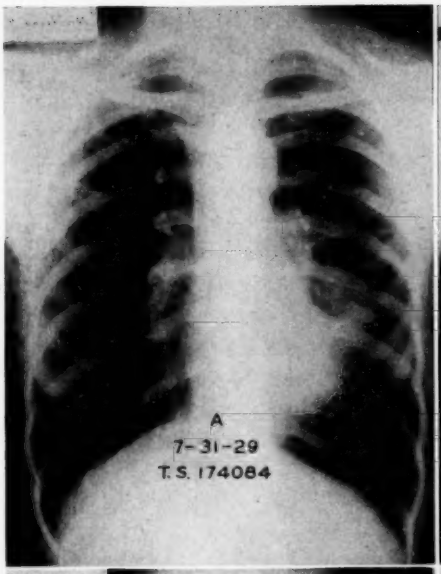
During the fall of 1930, four months before thoracoscopy, she had her first attack of dyspnoea and difficulty in both respiratory phases. The distress increased following pneumothorax refills. Attacks simulating asthma followed, consisting of paroxysmal cough, dyspnoea, and expectoration of thick, tenacious sputum. These attacks, which were becoming more frequent and severe, were described as coming on suddenly, producing dyspnoea, slight cyanosis, and a loud stertorous rattle, audible some distance from the patient.

Small refills were continued on the left but, due to increasing respiratory distress, she was transferred to the University Hospital in November, 1932, for investigation of the tracheobronchial tree. Physical examination at this time showed an inspiratory heave, harsh breath sounds beneath the angle of the right scapula, and in the left midaxilla "respiratory grunts and creakings," especially affecting the inspiratory phase, and suggesting to the examiner the possibility of bronchial obstruction.

Her course was gradually downhill; the attacks were not relieved by discontinuing the pneumothorax refills or by aspiration of air, and the lung re-

[2] Through the courtesy and kindness of Dr. George Leslie, Medical Director, Michigan State Sanatorium, Howell, Michigan, we have reproduced his films (figures 2A, B, C & D).

Fig. 2A



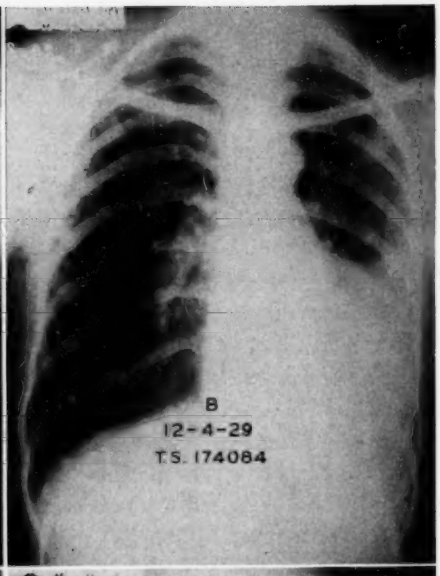
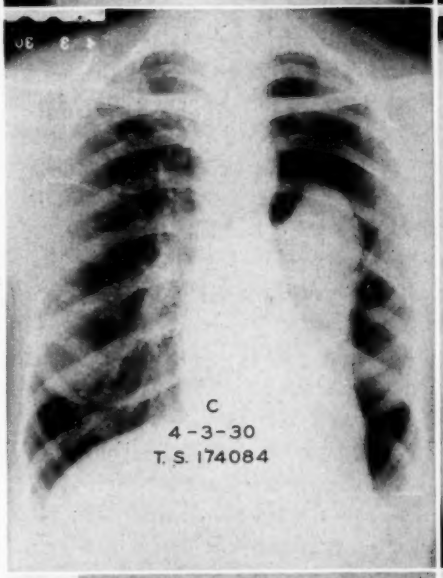


Fig. 2B

Fig. 2C



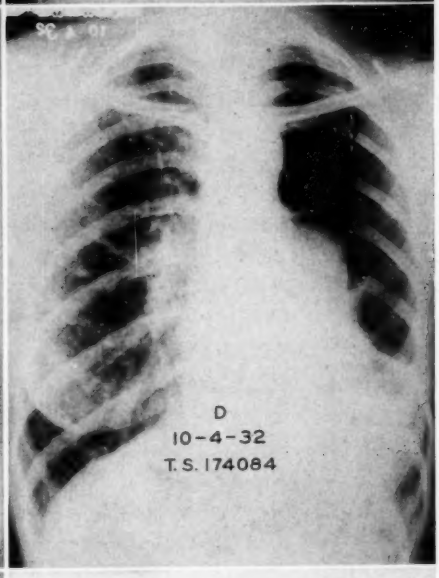


Fig. 2D

Fig. 3

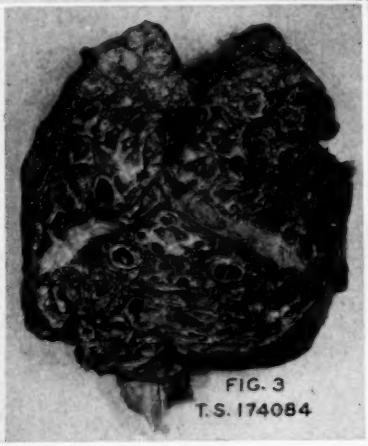


Fig. 4

mained completely collapsed. Bronchoscopy (Dr. Jones) on December 30, 1932 showed a normal upper trachea. One inch above the carina, the mucosa was thickened and the lumen narrowed, a stenosis being present. This took the form of a nonulcerating, circular, infiltration barely admitting the large aspirating tip. The area beyond the carina would not admit the bronchoscope. Aspirated secretions were loaded with acid-fast bacilli. The situation became desperate, and a low tracheotomy (Dr. Maxwell) was performed for the purpose of inserting a long tracheotomy tube, which gave some relief; and to minimize the trauma of the six bronchoscopies (Drs. Furstenberg, Canfield, Maxwell and Beavis), necessitated during the three days before death for the removal of crusts from the bed of a large ulcer in the left main stem bronchus and the unsuccessful attempt to dilate the stenosed left bronchus.

Case 2

Fig. 2A. Left lung shows light scattered tuberculous infiltration from apex to third anterior rib; homogeneous density off left border of heart.

Fig. 2B. Trachea, mediastinum and heart retracted to left. Homogeneous density at left base is probably atelectasis of lower lobe.

Fig. 2C. Atelectasis both left lobes six weeks following induction of pneumothorax. Heart in normal position.

Fig. 2D. After thirty-two months of pneumothorax. Two months before death. End of progressive retraction of left lung. Elevation of left diaphragm due to interruption of left phrenic nerve.

Fig. 3. Contracted left lung, equivalent in size to the cadaver's fist. Dilated bronchi occupy large share of total cut surface.

Fig. 4. Section through trachea showing irregularity of tracheal wall due to ulceration, A. Section through bifurcation shows disproportion in size of lumina of left bronchus B and right bronchus C.

Death occurred on April 1, 1933, five years and seven months after the onset of the bronchial symptoms, three and one half years following left pneumothorax and paralysis of the left hemidiaphragm, and three and one half years following the onset of acute respiratory distress.

Autopsy (Dr. Weller) revealed left sided pneumothorax with a completely collapsed and atelectatic left lung; equivalent in size to the cadaver's fist. It had a solid consistency and did not float in water. Longitudinal section showed the bronchi so close together that they appeared to make up about one half the tissue present (figure 3). The bronchi were markedly thickened with a rough, granular mucosa, and the lumina were filled with a thick mucoid, gelatinous material that protruded above the cut surface like well-formed molds of the bronchial lumen. The left main bronchus was markedly stenosed, being about six millimeters in diameter with a rough granular mucosa and irregularly shaped areas of ulceration (figure 4). The entire mucosal surface of the trachea was roughened and granular with diffuse ulceration and necrosis.

The right lung was uniformly emphysematous and pink except at the dependent portion of the lower lobe where it was firm to palpation and purple in color.

3: No. 205324, D. W., white, girl of 17 years, was admitted to the University Hospital October 29, 1928, complaining of cough and pain over the left chest. The diagnosis of pulmonary tuberculosis was established on physical findings and X-rays. The first twelve months of bed-rest were attended with slight change in the X-rays, but from the thirteenth to the fifteenth month there were rapid bilateral increases. Pneumothorax was induced on the left in January, 1930, after the first finding of tubercle bacilli in the sputum. Right pneumothorax was induced in May of the same year.

The second year was somewhat more satisfactory, serial chest films showing increase in bilateral pneumothorax and evidence of clearing of the partially collapsed lungs in spite of numerous bilateral adhesions. During this period several examiners reported rhonchi that were quite distressing to the patient. In October, 1930, dyspnoea became a little more marked following refills and in December, 1930, dyspnoea was further increased as was the cough and sputum, which was occasionally blood streaked.

In October, 1931, she was transferred to the Michigan State Sanatorium with continuation of the same treatment. She did quite well until January, 1932, when weight loss, increase in cough and sputum, and difficult expectoration developed, the latter following pneumothorax refills. Removal of air from the pleural cavity occasionally gave slight relief. She was returned April 20, 1932, to the University Hospital in extreme dyspnoea and, during laryngoscopic examination (Dr. Maxwell), a large inspissated plug of mucus and fibrin, one and one-half inches long, was removed from the trachea with immediate relief. She was returned to the State Sanatorium, where bilateral pneumothorax was continued. In August, 1932, she began to have attacks of rattling and stertor in the throat and expiratory difficulty. Expectoration of thick, tenacious sputum produced some relief. The respiratory distress increased, and loud tracheal rattles were audible in the patient's room. She was admitted a third time to the University Hospital, where bronchoscopy (Dr. Canfield) showed a diffuse ulcerative tracheitis with narrowing of the lumen of the lower trachea and the bronchi. A biopsy of the mucosa showed caseous tuberculosis.

The attacks of dyspnoea, wheezing, cyanosis, paroxysms of coughing and expectoration of thick, tenacious sputum continued. Bronchial and bronchovesicular breathing were clearly audible on the left. Breath sounds were absent on the right, but many râles, rhonchi, and wheezes were heard in both phases of respiration. The clinical impression was obstruction to the right main bronchus. A second bronchoscopy (Dr. Canfield) showed an ulcerating,

obstructing lesion in the right main bronchus, with pieces of moving slough attached to the edges. These were removed with marked symptomatic relief. The tracheal mucosa was considerably improved when compared with the examination of one month previously, patches of hyperaemia being noted, but no ulceration.

The distribution of many string-like adhesions suggested the possibility that torsion of the bronchi and their branches added to the existent respiratory difficulty. Consequently, the right pneumothorax was abandoned, resulting in rapid dissemination throughout the right lung and the development of a cavity. The left pneumothorax was continued, and, prior to again returning to the State Sanatorium, bronchoscopic examination (Dr. Canfield) was repeated. The tracheal mucosa was intact, showing only roughening; the right bronchus contained purulent discharge, the mucosa being hyperaemic, but free from crusting ulcerations, as previously noted. The left bronchus appeared normal.

For eight months before final admission to the University Hospital, she noticed that the slightest exertion brought on distressing respiratory symptoms. Her sputum continued thick and tenacious, constantly containing tubercle bacilli.

The fourth bronchoscopic examination (Dr. Jones), done one month before death, showed a sclerotic, scarred mucosa, and narrowed lumen of the entire tracheobronchial tree. The lobe orifices and both stem bronchi appeared stenosed, as if by fibrosis and scarring, this being more marked on the right. No ulcerations were seen.

Her subsequent course was progressively downhill, being marked by increasing expectoration, daily fever, tachycardia and embarrassed respirations. Death occurred September 14, 1933, five years after the onset of dyspnoea and three and a half years following institution of bilateral pneumothorax. Permission for autopsy was refused.

4: No. 309768, L. H., white, woman, age 27 years, was admitted March 10, 1933, complaining of cough and "rattle in the throat." The onset was insidious with ease of fatigue and weakness antedating admission two and one-half years. A sudden attack of wheezing, diagnosed as asthma (no X-ray taken) occurred one year before admission. No subsequent wheezing occurred, but the patient was conscious of an irritation in her throat resembling a "rattle," more pronounced in the supine position. Weight loss, night sweats and cough developed two months before our first examination. On physical examination, a lag on the right, palpable and audible rhonchi in the right apex anteriorly, first to third ribs, and friction rub in the right axilla were noted. The diagnosis of pulmonary tuberculosis was based on X-ray findings, March 29, 1933, of a unilateral lesion involving the right upper lobe (figure

5A), and positive sputum. April 1, 1933, a temporary paralysis of the right hemidiaphragm (Dr. Haight) was done and on April 20, 1933, an X-ray (figure 5B) showed the rise of the right diaphragm and atelectasis of the right upper lobe. This effected no change in symptoms but the sputum disappeared or contained no tubercle bacilli until July when tubercle bacilli were again found.

In September, 1933, there was a definite clinical change, cough becoming more severe, and thick, tenacious sputum increasing in amount. She experienced mild respiratory distress and audible wheezing. On one occasion during a severe paroxysm of coughing, a mucous plug the size of the tip of the little

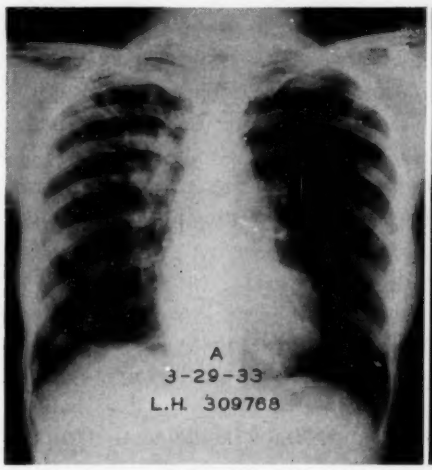


Fig. 5A

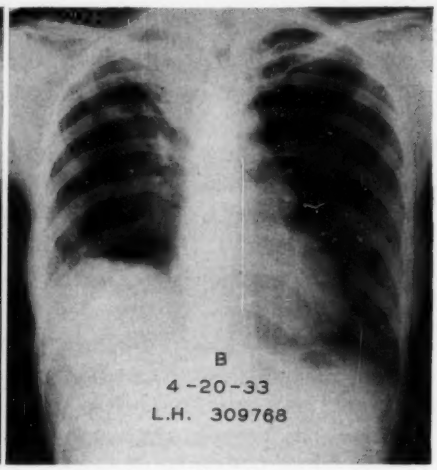


Fig. 5B

Case 4

Fig. 5A. Infiltration of the right lung as it appeared four days before paralysis of the right diaphragm.

Fig. 5B. Atelectasis right upper lobe. Elevation right diaphragm, nineteen days after crushing right phrenic nerve. The mottling seen in A in the second anterior interspace has disappeared into the atelectatic lobe. (See also figures 1 A, B, C and D.)

finger was expectorated, which gave marked but temporary relief from symptoms. Physical examination revealed palpable rhonchi, coarse râles and wheezes in the right upper chest, both anteriorly and posteriorly, with transmission to the left. At this time, the patient lost weight and had elevations of temperature to 100°F. By September 29, 1933, the atelectasis had disappeared leaving little evidence of a parenchymal lesion. A week later, bronchoscopic examination (Dr. Jones) showed the entire length of the tracheal lumen narrowed, the mucosa being scarred, and multiple ulcerative lesions with considerable crusting were seen. The right main stem bronchus was narrowed

with a similar type of lesion and the bronchoscope could not be safely passed. The left main bronchus was stenosed, but admitted the bronchoscope, the mucosa being ulcerated, scarred and thickened. Relief from the distressing wheezing and decrease in cough and sputum followed this procedure.

A short time later, the patient was removed to the West in the hope that dryness and altitude (5000 feet) would be beneficial. Two years have elapsed, and only in recent months have bath-room privileges been allowed twice daily. During the past year she has been free of cough and expectoration, but still experiences, at infrequent intervals, mild wheezing.

During the hospitalization here, the treatment consisted of bed-rest and temporary paralysis of the right hemidiaphragm. Ultraviolet light irradiation and numerous cough mixtures were tried without beneficial results. When tested intracutaneously, the patient was not hypersensitive to three autogenous vaccines made from *Streptococcus viridans*, *Streptococcus haemolyticus* and *Micrococcus catarrhalis*, isolated from the sputum, nor to a vaccine of a gram-negative intracellular diplococcus isolated from the bronchoscopic aspirations from case 3. Subcutaneous tuberculin therapy was begun here and continued in the West with the addition of calcium gluconate. The expectoration of a small mucous plug and bronchoscopy were the only incidents followed by a definite change toward improvement.

5: No. 323608, L. G., white, woman, 33 years of age, was admitted January, 1934, complaining only of cough and fatigue. The onset had been insidious and the duration seven months. Examination revealed an impaired percussion note over the left apex, râles in the left axilla and tubercle bacilli in the sputum. Chest X-rays, February 6, 1934 (figure 6A), showed a density fanning out from the left hilum with a small area of mottling in the periphery at the third anterior rib. The right lung was clear. Three previous X-ray examinations in the out-patient department, October and December, 1933, and January, 1934, had shown the same appearance as was seen in February, 1934 (figure 6A). A temporary paralysis of the left hemidiaphragm (Dr. Streider) was done February 17, 1934. The X-ray of March 8, 1934 (figure 6B) showed a smooth density in the right anterior second intercostal space, elevation of the left dome of the diaphragm, and an increase in shadows in the axilla at the level of the third and fourth anterior ribs, with sharply defined borders replacing the irregular mottling. One week later, a left pneumothorax was instituted, resulting in immediate collapse, partial atelectasis of both lobes and pleural effusion (figure 6C). Attention is called to the rapid appearance (figure 6B) and disappearance (figure 6C) of the density in the right second intercostal space, which had not been present in figure 6A.

Sixty to seventy per cent collapse of the left lung was maintained for four months (figure 6C), and the pleural cavity again became dry. Per-

Fig. 6A

Fig. 6B

Fig. 6C

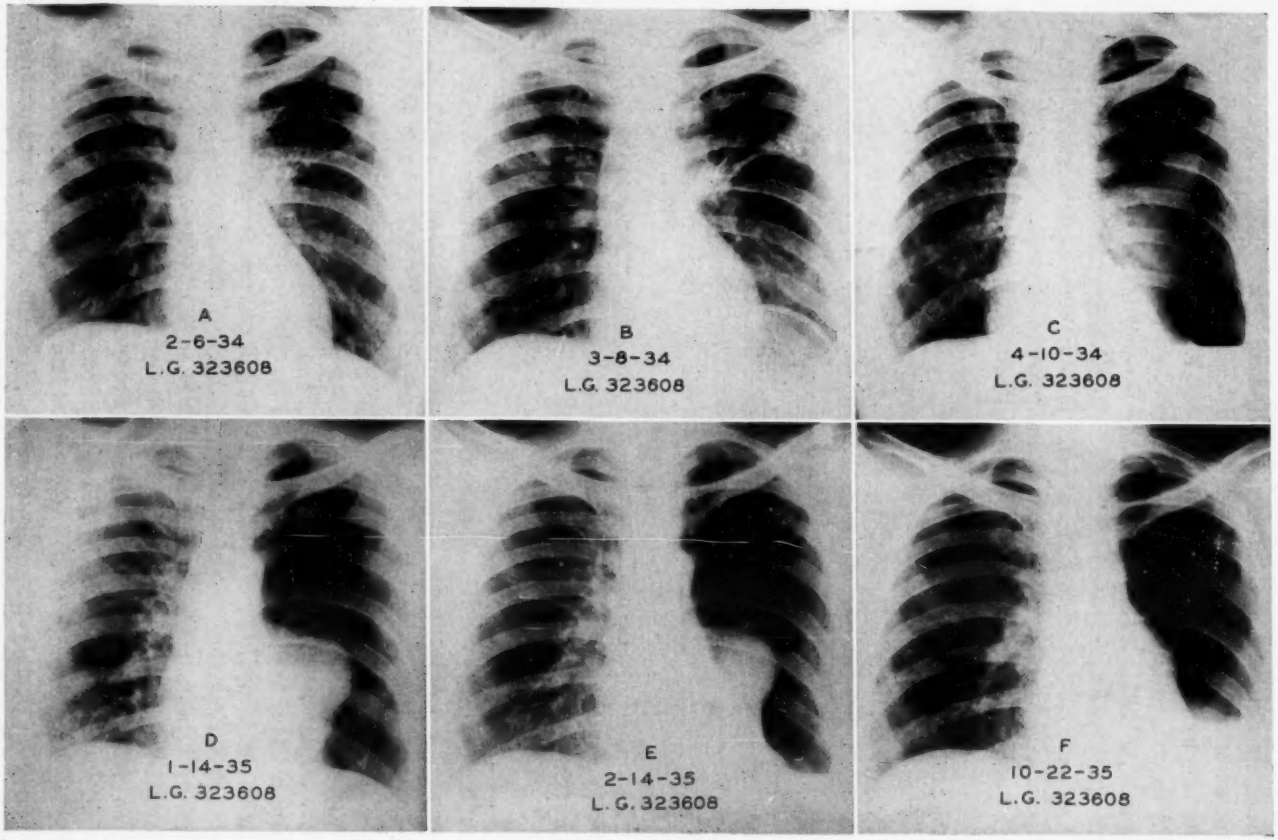


Fig. 6D

Fig. 6E

Fig. 6F

sistence of adhesions, preventing collapse of the peripheral lesion, and bacilliferous sputum led to cauterization of adhesions, August 8, 1934, by closed intrapleural pneumonolysis (Dr. Alexander). The left lung was now completely collapsed (figure 6E) but still the sputum contained tubercle bacilli, and the patient was mildly cyanotic. It was at this time that questioning readily brought out the fact that the patient had experienced "wheezing" and "rattling" localized to the left upper lung during the seven months before her admission and throughout her hospitalization, unknown to the staff or referring physician. Examination at this time revealed loud expiratory parasternal rhonchi on the left, which could not be dislodged by cough, though

Case 5

Fig. 6A. Minimal infiltration left root and in periphery at left third anterior rib. Tubercle bacilli in sputum. There is no change between shadows seen in A, from those seen in serial X-rays taken from October, 1933 to January, 1934, while patient was ambulatory.

Fig. 6B. Development of small area of atelectasis in right second anterior interspace. This shadow was not present one month earlier in A, nor one month later in C. Elevation of paralyzed left diaphragm, resulting in cone-shaped area of atelectasis at left third anterior rib.

Fig. 6C. Area of atelectasis in right lung field seen in B has disappeared and remains absent in monthly X-rays for the next eighteen months. Hydropneumothorax on left, collapse of both lobes with adhesion in region of original lesion. Tubercle bacilli persist in the sputum. Last refill April 9, −6−4, 250 cc., −4−1. In the left axilla may be seen a haemangioma of chest wall protruding into pleural cavity.

Fig. 6D. Left lower lobe is completely collapsed and has been so since intrapleural pneumonolysis in August, 1934. The left upper lobe (it has dropped to the base of the thorax—its border is seen parallel to the border of the collapsed lower lobe and midway between it and the thoracic wall) is now expanded, though the X-ray two months before showed it completely collapsed, as it is again in E, taken one month later. Tubercle bacilli remain in the sputum. Last refill January 10, −8−3, 300 cc., −5−1.

Fig. 6E. Both left lobes completely collapsed, one month after expansion of left upper lobe in D. Tubercle bacilli remain in sputum. Last refill January 31, −11−6, 300 cc., −7−4.

Fig. 6F. Left lung has remained completely collapsed. Inspiration and expiration X-rays show no change in contour of left lung. Left lung now shrunken, much smaller than when first collapsed. Tubercle bacilli in the sputum. Febrile pleural effusion on left has intervened since E. Last refill October 7, −9−3, 100 cc., −3+1.

this finding had never been reported in any of the previous two dozen routine physical examinations. A clinical diagnosis of bronchial obstruction was confirmed by bronchoscopy (Dr. Furstenberg) on January 12, 1935, which showed the bronchial tree on the right to be entirely normal. On the left, however, there were ulcerations of the mucosa and exudate, but the most prominent feature was a large, red fungating tuberculoma arising from the wall of the bronchus. The lumen was entirely filled except for a narrow crescent-shaped passage. The bronchoscopy had no influence on the patient's progress, but the symptoms and signs of obstruction had disappeared spontaneously shortly before the examination.

Fig. 7A

Fig. 7B

Fig. 7C

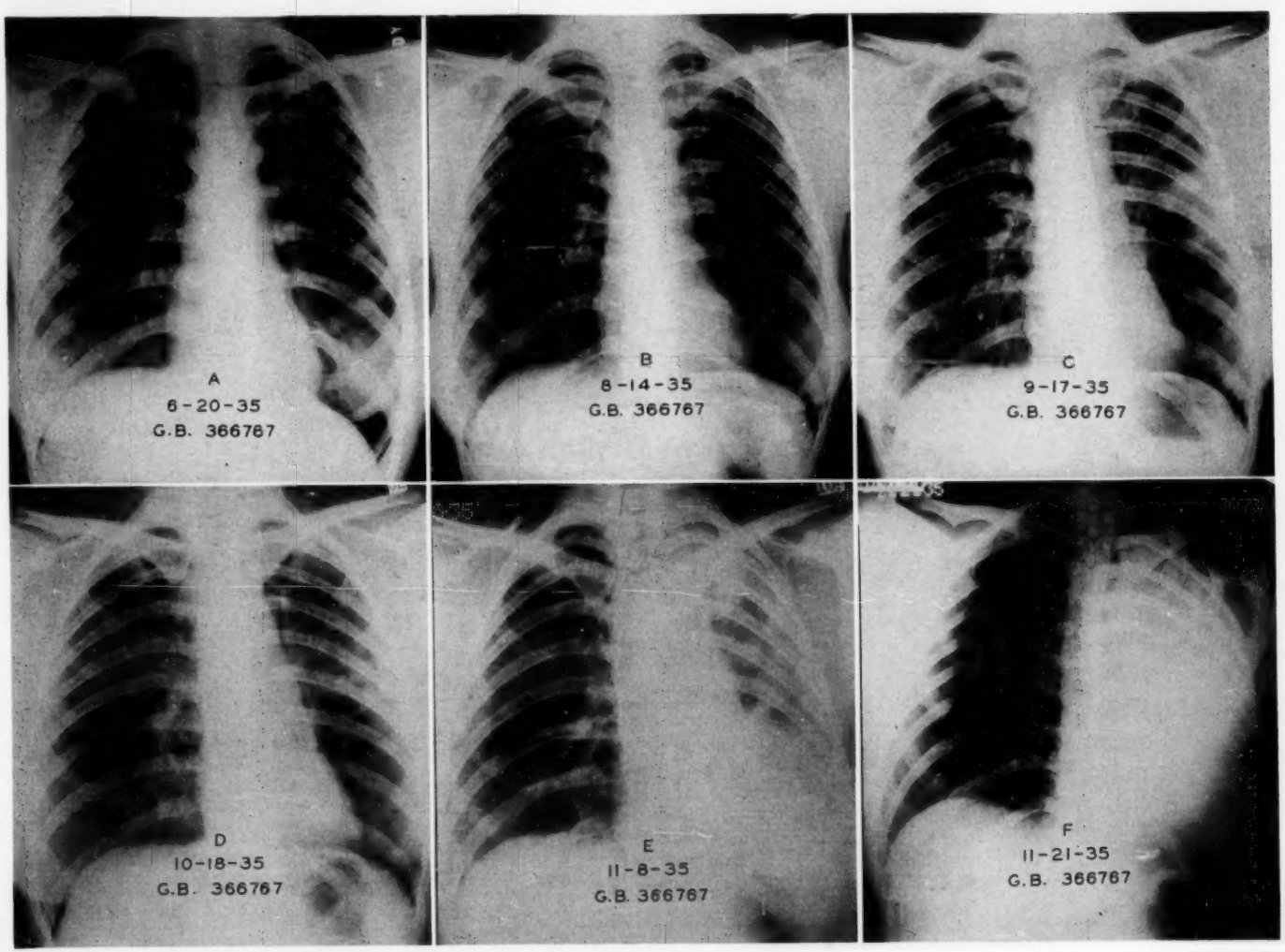


Fig. 7D

Fig. 7E

Fig. 7F

A series of medium wave-length roentgen treatments were begun on January 22, 1935, and continued at weekly intervals over the upper thorax, alternating anteriorly and posteriorly. Following the seventh X-ray treatment on March 4, pleural effusion with fever developed, lasting three months. The patient lost weight and appeared more cyanotic.

Six months following the first bronchoscopy, a second examination (Dr. Furstenberg) was done, and marked improvement was noted on the left. The right side remained normal. This second bronchoscopy was not done until the patient had begun a general clinical improvement which has continued. The bronchial symptoms remained absent from January, 1935, until August, when there were "wheezes" for only eight days. Temperature remained normal except for sharp rises of from 102° to 103°F. on the day following pneumothorax refills or fluid aspirations. These temperature ele-

Case 6

Fig. 7A.[3] There is only a suggestion of abnormal shadow in the left lung just above and just below first anterior rib peripherally. Tubercle bacilli were found in the sputum at this time.

Fig. 7B. First out-patient visit eight months after onset. Tubercle bacilli in sputum. Minimal infiltration in left apex to second anterior rib, showing slight increase in the two months since A, during which time patient was ambulatory. Mediastinal structures and diaphragm in normal position.

Fig. 7C. Eighteen days after bronchoscopy a shadow has appeared in left midlung field peripherally, where there was previously no involvement. The sudden appearance, sharpness of borders suggest atelectasis, though there is no shift of mediastinal structures or diaphragm.

Fig. 7D. One month after C. Shift of mediastinum and heart to left and shrinkage of shadow in left midlung field.

Fig. 7E. Ten weeks after bronchoscopy, five weeks after beginning X-ray treatment. Elevation of left diaphragm, further shift of mediastinum to left, additional areas of atelectasis at apex and base.

Fig. 7F. Atelectasis of left lung practically complete, three months after admission.

vations became less and less frequent. The sputum has contained tubercle bacilli almost constantly, but in fewer numbers over the past three months.

November 2, 1935 a third bronchoscopy, by the same examiner, showed again the small superficial ulcer on the lateral wall of the left bronchus, two centimeters below the carina. At a deeper level, the tuberculoma, springing from the lateral wall of this bronchus, appeared about one-third its original size.

Twenty-three months sanatorium care, four months of sixty to seventy per cent collapse, sixteen months of total collapse of the left lung (figures 6D, E & F) have failed to obliterate tubercle bacilli from the sputum.

6: No. 366767, G. B., white, woman, age 37 years, was admitted August 19, 1935, complaining of cough, weakness, fatigue, and a "rattle in her throat

[3] X-ray furnished through courtesy of Dr. E. W. Meredith, referring physician.

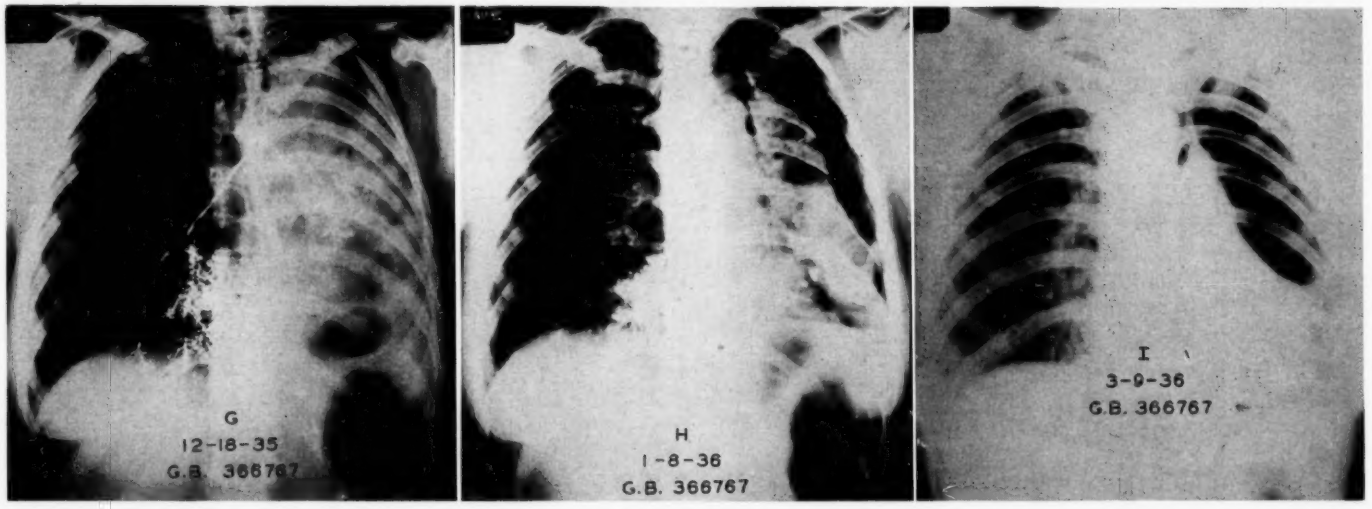


Fig. 7G Fig. 7H Fig. 7I

Case 6

Fig. 7G.[4] Lipiodol filling. The trachea is deviated to the left. The right main stem and lower lobe bronchus are patent and filled to the terminal bronchus. The left main stem is narrowed and irregular. The lipiodol penetrates but to a short distance beyond the bifurcation as compared to penetration on the right. The heart is displaced to the left and left diaphragm is elevated, but some areas of aeration remain in left lower lung field.

Fig. 7H. Film taken on day of induction of pneumothorax and injection of only 300 cc. of air. Atelectasis of lower lobe is more complete than in upper lobe, though the upper lobe was the original site of disease, only five months previously.

Fig. 7I. Atelectasis of left lung practically complete in spite of adhesions to apex and base, two months after induction of pneumothorax. Compare figures 2A, B, C and D and figures 6B, C, D and E.

[4] Films for figures 7G, H and I furnished through the kindness of Dr. D. O. N. Lindberg.

and upper left lung." The onset of the present illness was in January, 1935, with what the patient called "flu." The symptoms were weight loss, fatigue, malaise, temperature to 102°F., heavy feeling in the anterior chest, and cough productive of small amounts of sticky sputum that were raised with difficulty. During May, 1935, the patient first experienced wheezing and noticed a "rattle in her throat and upper left lung." She could feel this "rattle" or "rumble" with her hand anteriorly over the left apex, and it was audible to her husband some distance from the patient. These phenomena, suggestive of bronchial obstruction, became very annoying and frightening to the patient, especially at night, and were solely responsible for her first consulting a physician. A letter from the referring physician, Dr. E. W. Meredith, Port Huron, Michigan, brings out some of the difficulties of diagnosis. "At the time of her first visit to me in May the chest sounded more like an asthmatic bronchitis. There were no tubercle bacilli found in the sputum at that time, and there were no definite X-ray evidences of parenchymatous involvement of the lungs (figure 7A). There was an increased density of root shadows especially on the left side. Repeated examinations of the sputum, however, showed tubercle bacilli."

She rested at home until her admission here three months later, and during this period the previous symptoms continued. In addition she had some shortness of breath, temperature rises to 99.4°F. and occasional night sweats.

Our first examination showed palpable rhonchi over the left chest, coarse râles and wheezes loudest in the left axilla and over the base of the left lung posteriorly. Breath sounds were difficult to hear because of numerous asthma-like wheezes. Tubercle bacilli were again demonstrated in the sputum, and chest X-ray, August 14, 1935 (figure 7B), showed a light minimal infiltration in the left apex to the second anterior rib.

A clinical diagnosis of tuberculous tracheobronchitis, complicating pulmonary tuberculosis, was immediately entertained, and a few days later, August 30, 1935, the bronchoscopist (Dr. Samson) found an ulcerative tuberculous tracheobronchitis and slight stenosis of the left stem bronchus at its orifice. Symptomatic improvement followed, the wheezing and "rattling" gradually disappeared, the cough became less distressing, and expectoration easier.

September 17, 1935, X-ray (figure 7C) showed a new shadow in the left midlung field peripherally with sharply defined borders. No new physical findings were detected at this time and the temperature, pulse and respirations were normal.

Sanatorium care and strict bed-rest made up the treatment till October 3, when a series of five medium wave-length roentgen ray treatments were begun, alternating over the upper anterior and posterior thorax at weekly intervals. October 18, 1935, X-ray (figure 7D) showed a shift of the medi-

astinum and heart to the left and shrinkage of the shadow in the left mid-lung field. Three weeks following the beginning of X-ray treatment marked changes were noted in the physical findings of the chest. The left lung was resonant, but there was a complete absence of tactile fremitus, breath sounds and voice sounds. Approximately at the same time elevations of temperature (98.6° to 103°) and pulse (80 to 130) occurred and continued until the time of discharge, November 23, 1935.

November 8, 1935, she complained of pleuritic pain in the left axilla, and a transient friction rub was detected in the third intercostal space anteriorly. The left upper lung field was resonant anteriorly and posteriorly, breath sounds, tactile fremitus and voice sounds being transmitted over this area. Posteriorly, below the sixth dorsal spine, there was flatness, absent tactile fremitus, breath sounds and voice sounds. A demonstrable shift of the mediastinal structures to the left was found on percussion and palpation. X-ray (figure 7E), on the same date, showed a further shift of mediastinal structures, when compared with the previous month, and, in addition, elevation of the left dome of the diaphragm was noted for the first time. Areas of atelectasis now appeared at the apex and base of the left lung. The last X-ray (figure 7F) before discharge showed massive collapse of the left lung.

We are indebted to Dr. D. O. N. Lindberg, Decatur, Illinois, for the following data on the patient's postdischarge history and for permission to reproduce his X-rays (figures 7G, H & I).

"The sputum contained tubercle bacilli on December 2, (Gaffky V) and on December 4, 1935 (Gaffky II). The amount of air producing the pneumothorax seen on films dated January 8, 1936 (figure 7H) was 300 cubic centimeters. The first refill was given one day later and 450 cubic centimeters resulted in very little additional compression.... The next (concentration sputum) examination was made on February 6, 1936, or less than thirty days from time of institution of induced pneumothorax, and no tubercle bacilli were found.... She has gained four and one-half pounds in weight. She has been ... free (of fever) for two months. All constitutional symptoms are absent."

DISCUSSION

Extent of pulmonary lesion: One of the most striking features of this series of cases is the small extent of the pulmonary focus of tuberculosis when the patient first came under observation. The extent of the lesion seemed to have no parallelism with the severity of the symptoms or the downward course of the illness. Of the four patients who died of the complication of ulcerative tuberculous tracheobronchitis, two were classified as minimal when first seen and two were in the moderately

advanced group. Minimal and moderately advanced pulmonary tuberculosis is usually amenable to treatment of the simplest sort, but these patients progressed to death in spite of, or because of, every known method of giving rest to the body and to the diseased lung. Only one of our nine patients with ulcerative tuberculous tracheobronchitis was classified as far advanced on admission. Furthermore, only one of our cases had tuberculous complications outside of the respiratory tract, so that the failure of treatment cannot be ascribed to a general breakdown of bodily resistance to the tubercle bacillus. This fact is further borne out by the studies of autopsy material (Bugher, Littig and Culp (16)).

Tubercle bacilli in the sputum: It is not remarkable that all cases had tubercle bacilli in the sputum, but tubercle bacilli appeared and persisted in these cases under circumstances which we considered unusual. In case 6 tubercle bacilli were found in the sputum before an unequivocal roentgenological diagnosis could be made. At the time of the finding of the tubercle bacilli, there was no other point on which to base a diagnosis or even to form a presumption of tuberculosis. In other cases of minimal pulmonary tuberculosis, the sputum contained tubercle bacilli long beyond the usual period of treatment given to patients with minimal pulmonary tuberculosis. This fact led to the inauguration of a long series of collapse measures in case 5. The most serious disappointment has been the finding that collapse, even total collapse of the involved lung, has not rendered the sputum free of tubercle bacilli (cases 2 and 5). The conclusion must be drawn, and the bronchoscopic studies (Samson (15)) and the pathological studies (Bugher, Littig and Culp (16)) support the conclusion, that the tracheal and bronchial ulcers are a source of tubercle bacilli in the sputum. The bearing of this point on the indications for bronchoscopy and the indications for collapse therapy are dealt with in a subsequent section. The presence of tubercle bacilli in the sputum of patients whose pulmonary lesions, as revealed by the X-ray, do not fully explain the presence of tubercle bacilli in the sputum, should naturally arouse the suspicion that tracheal or bronchial ulcers exist.

The complication as the cause of the chief complaint: In three of our cases the wheezes, rattles and other symptoms of partial bronchial obstruction formed the chief complaints and the first symptoms of tuberculosis (cases 2, 4 & 6). In two the diagnosis of asthma had been made prior to admission. In all but one the symptoms of the complication

as contrasted to the usual symptoms of pulmonary tuberculosis remained the chief and dominating complaint throughout the patient's illness. In that one exception (case 5) the symptoms were so slight that the patient had been under treatment for a year before the complication was suspected.

Atelectasis[5] *as a feature of the complication:* The intriguing behavior of the right upper lobe in case 1, which was now atelectatic and again inflated in serial X-rays (figures 1A to D), first led us to investigate a bronchial cause for this phenomenon. We had expected to find a broncholith partially or completely occluding the right upper lobe bronchus. Instead the bronchoscopist found a large ulcer of the bronchus surrounded by oedematous mucous membrane. A biopsy confirmed the impression that the ulcer was tuberculous, though this was a needless and probably harmful addition in the presence of tubercle bacilli freely demonstrable in the sputum. That the right upper lobe had been intermittently atelectatic there could be no doubt, for as Dr. Henry Field, Jr. pointed out, whenever the homogeneous density appeared, the mottling in the first anterior interspace disappeared. The mottling in the first interspace could have disappeared nowhere else except into the atelectatic upper lobe, for whenever the shadow of atelectasis disappeared the characteristic mottling reappeared in the first interspace. This phenomenon appeared on many serial X-rays not reproduced in this report. The fact that there was no displacement of the trachea in this case, we believe, is evidence that atelectasis of a lobe may be compensated wholly by emphysema of other parts of the lung; and that displacement of the trachea should not be demanded as a criterion of atelectasis. When the position of the trachea is fixed by surrounding inflammation, the possibility of atelectasis is not removed; at autopsy the trachea in this case was so fixed. There was atelectasis then, and there was ulceration and oedema of the bronchus, and there were the symptoms associated with bronchial obstruction. The picture could be reconstructed only by assuming that the oedema was not constant in amount, and that when the oedema became intense the wall of the bronchus would be so thickened and in consequence the lumen so narrowed,

[5] The term *atelectasis* has been used here to describe the sudden development of airlessness in the presence of cause for bronchial occlusion. We believe that initially the condition will be pure atelectasis. It will probably not remain so in a lung with known tuberculous foci which is supplied by infected bronchi with drainage blocked. Autopsies obtained months after the onset will not yield evidence of the pure atelectasis that originally obtained.

that partial obstruction obtained. If, in addition, thick, tenacious sputum entered the narrowed lumen, the obstruction would become complete and varying degrees of atelectasis would be found in the next serial X-ray depending upon the time interval between the occurrence of the obstruction and the making of the X-ray exposure. Subsidence of the oedema or dislodging of the mucous contained in the lumen would allow inflation of the lobe. This seemed a likely explanation of the events observed and the hypothesis has served to interpret many changes seen subsequently in this and other patients.

If this could happen so readily in a major bronchus, it seemed all the more likely to happen in smaller bronchi. If it should happen in a smaller bronchus, there is the possibility that the collateral respiration, which Van Allen and Soo (17) found in healthy animals, would maintain aeration and prevent atelectasis in the area supplied by that bronchus. In tuberculosis of the bronchi there is every reason to suppose, however, that tuberculous disease of the parenchyma and its exudates frequently seal these channels to collateral respiration and so allow the possibility of localized or lobular atelectasis. Given tuberculous disease of the parenchyma and tuberculous processes in the walls of the bronchi capable of producing occlusion, we may expect to find areas of atelectasis of any size from very small anatomical subdivisions of a lobe up to that of a whole lobe or a whole lung. Such has been our interpretation of many of the shadows that we have seen in the X-rays of patients with ulcerative tuberculous tracheobronchitis.

In case 5 (figures 6A to C), a small density appears in the second right anterior intercostal space which was not present the month before and which leaves no remnant the month after its appearance. This is a reproduction on a small scale of the appearance and disappearance of lobar atelectasis in case 1. The suddenness of the appearance and of the disappearance is, we believe, good argument that it was atelectasis rather than infiltration.

In case 2 (figures 2A & B), we saw the development of atelectasis of the lower lobe, and in this case the diagnosis of atelectasis is supported by the retraction of the heart and the elevation of the diaphragm.

In case 6, we saw the development of atelectasis from the patchy, lobular stage (figure 7C) through the aggregation of other lobular areas to involve almost the entire left lung with only a few areas of aeration remaining (figures 7C to G). The diagnosis of atelectasis in the later X-rays is again supported by retraction of the trachea and mediastinal

structures and by the elevation of the diaphragm. We believe the earlier shadows were also atelectatic in origin because of their sudden appearance (figures 7B & C). Pulmonary tuberculosis, as usually seen in serial X-rays, does not behave in this fashion. The lesion did not extend from the initial lesion, as is usual; it did not appear in one of the usual sites for a bronchogenic dissemination; it had much more sharply defined borders than is seen in a tuberculous lesion of such recent origin; and it had a homogenous appearance. The whole left lung became dense with shadow in an extremely short time (there are only three months between B and F of figure 7); no cavities appeared; and it could not have been caseous pneumonia for retraction appeared early and increased as the shadows extended.

The lipiodol filling in figure 7G shows nicely how the swelling and thickening of the left bronchial mucosa has narrowed the lumen. The bronchi plugged with lipiodol are close to the bifurcation and normally have a much larger lumen than is shown in this film. The lipiodol in this instance demonstrates the possibility of thick sputum producing a similar plugging of such narrowed bronchi. Compare the wide lumen and the basal filling of the bronchi in the right lung.

Factors conducive to atelectasis: The pathological conditions present and their anatomical distribution in tuberculous ulcerations of the bronchi tend naturally toward the development of atelectasis. Physiological considerations suggest that many of the routine measures adopted to give rest to the body and the lungs in the treatment of pulmonary tuberculosis would favor the development of atelectasis in such cases. Anything which would tend to shorten the bronchi, and so relatively increase the thickness of the swollen mucous membrane, would narrow the lumen and enhance the likelihood of obstruction and consequent atelectasis. The length of the bronchi is decreased in the midposition of respiration by placing the patient at bed rest and discouraging deep breathing and other respiratory effort; the bronchi are further shortened by any and all methods of collapse of the lung. A third possible factor in our treatment of these cases that has contributed toward the development of atelectasis has been the use of X-ray therapy. If X-ray therapy produces some immediate swelling of the inflamed mucosa, then the additional thickness of the bronchial wall might be sufficient to cause bronchial obstruction and therefore atelectasis. A fourth possibility in our cases is that the trauma of the bronchoscopic examination may have produced the necessary swelling to occlude the bronchus. The

bearing of each of these four factors on the cases reported is discussed separately in the succeeding paragraphs.

Bed-rest and hypoventilation: Surgical experience with postoperative atelectasis indicates that shallow breathing is a factor in the production of atelectasis. The type of rest given routinely to patients first admitted to sanatoria for the tuberculous is designed to reduce the respiratory effort to a minimum. If a patient with a swollen bronchial mucosa is placed on such a regimen of enforced rest, and if beyond the point of the swelling in the bronchus there is a source for secretions, it is not surprising that the concurrence of these factors should be attended by the first production of atelectasis.

Case 2 had complained of rattles in the chest for at least two years before sanatorium treatment was instituted. In that period of two years, X-rays taken at the beginning and the end of the period showed little change in a minimal basal lesion. After four months of bed-rest, with no other treatment and before bronchoscopy was done, there was massive atelectasis of the left base.

Case 5 had experienced wheezing for five months before admission to the hospital, and had been observed by serial X-rays for three months as an out-patient without the development of atelectasis and with no change in the parenchymal lesion. Within a month of the inauguration of strict bed-rest in the hospital, transient atelectasis developed in the right lung which received no collapse therapy and before bronchoscopic examination was done.

The effect of bed-rest in case 6 is less definite as X-ray evidence of atelectasis did not appear until after the bronchoscopy, but it can be said that the course of the disease was worse after the institution of treatment than it had been before admission to the hospital. She had had symptoms of the complication for six months before the first X-ray examination (figure 7A) which showed no evidence of atelectasis and little evidence of any disease. At the time of admission, the duration of the disease had been eight months, and the X-ray (figure 7B) still gave no evidence of atelectasis. Within three months of the institution of treatment, atelectasis of the left lung was nearly complete (figure 7F).

Production of atelectasis by collapse therapy: Collapse of the lung by any method results in some relaxation of the lung and some shortening of the bronchi. This is obvious in lungs collapsed by pneumothorax, thoracoplasty and paraffin pneumonolysis when the X-rays actually show the lessened distance between the root and the periphery of the

lung in at least one plane. In paralysis of the diaphragm, it is obvious only in basal lesions when the distance between the lesion and the root of the lung can be shown to be shortened at least in inspiration. We believe, however, that a similar effect can be demonstrated in many upper lobe lesions, when the shortening of the distance between root and periphery is affected by an elevation of the root. There is the additional factor of distortion of the bronchi by reason of a change in the direction of their axes following many forms of collapse.[6]

Shortening of the bronchi by collapse naturally does not affect the diameter of the cartilagenous rings and the outer wall of the bronchi. In ulceration of the mucous membrane, there is, however, an associated swelling and oedema as is shown in the lipiodol filling in case 6 (figure 7G) made before the institution of collapse. When the bronchi are shortened by collapse, this swollen bronchial lining is thickened by the gathering up of its length into a shorter space. The bronchial lumen may be sufficiently narrowed by this mechanical action alone to produce obstruction and atelectasis, without the probable additional factor of thick secretions plugging the narrowed lumen. Four of the six cases chosen for this report illustrate this effect of collapse therapy in the presence of ulcerative tuberculous tracheobronchitis.

Paralysis of the diaphragm: The symptoms of partial bronchial obstruction had been present in case 4 for a year before admission; yet there was no evidence of atelectasis in the admission X-ray (figure 5A). Nineteen days after paralysis of the right diaphragm by crushing the nerve, atelectasis of the right upper lobe is present in the X-ray (figure 5B). This response to phrenic paralysis is in accord with our hypothesis and it has appeared to us as so typical that its occcurrence should suggest the possibility of tuberculous tracheobronchitis.[7]

There is some indication that a similar effect followed diaphragmatic paralysis in case 5. The changes in the shadows in the left lung in figure 6 between A and B suggest that atelectasis has taken place fol-

[6] When Dr. T. T. Wang of the Peiping Union Medical College was visiting this clinic, he was shown the X-rays on case 4. He said that he and Dr. C. M. Van Allen had entertained this hypothesis and had construed it as a contraindication to collapse therapy when bronchial disease was present.

[7] This typical response to phrenic paralysis was noted in the serial X-rays sent to Dr. Kirby S. Howlett, Jr., then a member of the staff of this hospital. In writing his report of the X-rays, Dr. Howlett mentioned our suggestion that the X-rays gave some evidence that bronchial occlusion had followed the phrenic paralysis. Dr. Howlett later heard from the referring physician that bronchoscopy had confirmed the diagnosis of ulcerative tuberculous tracheobronchitis. This diagnosis had been hazarded on the evidence in the X-rays alone.

lowing the elevation of the diaphragm. In B, the shadow has more sharply defined edges and it is triangular in shape.

Even though the diaphragm is not elevated enough to effect changes in the direction of the bronchus or changes in the bronchial length, the effect of the paralysis on the depth of respiration might be sufficient to allow occlusion of the thickened bronchial walls.

Atelectasis in pneumothorax: The X-ray picture of tuberculous areas of the lung collapsed by pneumothorax is often indistinguishable from areas of atelectasis. The collapsed areas probably contain both areas of atelectasis and areas of tuberculous pneumonia which form one homogeneous shadow. These homogeneous densities, however, always appear in the lobe and usually in that part of the lobe which showed the tuberculous involvement before the pneumothorax was induced. This is a common picture in selective collapse by pneumothorax. The selective collapse may be confined to one lobe or to only a part of a lobe; the parts of the lung which were free of disease remain aerated as long as the intrapleural pressures are kept subatmospheric. The collapse of the diseased areas seems to be due to retractile forces inherent in the diseased tissue; it is not due to bronchial obstruction since drainage from the area remains free and cavities empty themselves of their secretions which are expectorated.

We have never seen the picture just described of selective pneumothorax in patients with ulcerative tuberculous tracheobronchitis. Instead of selective collapse of the involved area of the lung only, we have witnessed rather sudden and total collapse of a whole lobe or of a whole lung even though the lesion before pneumothorax occupied only a very small part of one lobe. The suddenness of the collapse has been as conspicuous as the totality of the collapse. In the absence of bronchial occlusion, pneumothorax allows a rather slow progressive collapse of the involved areas. When pneumothorax shortens the bronchi and allows the thickened walls to obstruct the bronchus, a very marked degree of collapse is found at the very next fluoroscopic or roentgenographic examination.

In case 2 (figure 2) the original disease and the atelectasis existing before the pneumothorax was induced were confined to the left base, while the left upper lobe remained clear in every X-ray taken over a period of two and a half years. The first X-ray, taken only two days after induction of the pneumothorax, showed an airless left upper lobe which had never before been involved.

In case 5 the original lesion was confined to a very small area in the left lower lobe (figures 6A & B). In the absence of bronchial occlusion, one would expect pneumothorax to permit selective collapse of this small area; but one would expect the remainder of the lower lobe to remain aerated while negative intrapleural pressures prevailed. Instead, both lobes became almost completely atelectatic (figure 6C). After the adhesion to the lower lobe was severed by cautery, this lobe never again became aerated, though the intrapleural pressures were well subatmospheric. The upper lobe, which had been free of disease, behaved curiously, for, in serial monthly X-rays, it would be atelectatic on one occasion and aerated on the next. The intermittent atelectasis of the left upper lobe repeated itself through a long series of serial X-rays, two of which are reproduced (figures 6D & E). The behavior of this upper lobe resembled that of the right upper lobe in case 1 (figures 1A, B, C & D). In addition to the factors responsible for the inconstancy of the atelectasis in case 1, there was, in this case (case 5), the variations in intrapleural pressures and consequent variation in length of the bronchi. The more negative the intrapleural pressures, the greater the pull on the lung; and this pull stretches the contained bronchi and so thins the mucosal wall to the point that air might enter the lobe. When a refill of air would reduce the intrapleural pressures below this critical level, the bronchial walls would come in contact and produce occlusion.[8] The nature of the collapse in case 5 was one of the elements which led to the clinical diagnosis of tuberculous tracheobronchitis and bronchoscopic examination.

The atelectasis was practically complete in case 6 (figure 7) before pneumothorax was induced, but it is interesting that the response of this lung to pneumothorax was predicted before the attempt was made.

[8] A patient, not included in this series because of her inability to coöperate during an attempted bronchoscopy, had all the signs, symptoms, and X-ray characteristics of obstructive atelectasis of the right upper lobe due to tuberculous bronchitis. Cavities, seen in the right upper lobe in X-rays previous to admission, had disappeared in the admission X-rays. The right upper lobe was represented only by a narrow rectangular density extending from the root upward along the shadow of the spinal column. Pneumothorax on the right failed to influence the symptoms or the sputum. After a year, reëxpansion of the pneumothorax resulted in an exacerbation of all the symptoms. The right upper lobe reëxpanded under high negative pressures, and the cavities reappeared. When pneumothorax refills were resumed after a two months lapse, the right upper lobe again became atelectatic. The patient was improved symptomatically, but tubercle bacilli remained in the sputum.

Case 3 of this series showed a similar harmful reaction to reëxpansion of a lung collapsed by pneumothorax for three years.

Medium-length roentgen-ray therapy: We have personally observed two patients with tuberculous ulcers of the trachea and bronchi that were subjected to medium wave-length roentgen-ray treatment.[9] In one of these (case 6, figure 7) there is the suggestion that the treatment contributed to the rapid development of atelectasis. Some atelectasis had developed after the bronchoscopy and before the roentgen-ray treatments were begun (figure 7C). Within six weeks of the beginning of the treatment, atelectasis of the entire lung was practically complete (figure 7F), and the treatments had to be discontinued because of the symptomatic response. The evidence of the swollen mucosa is amply demonstrated in the lipiodol filling (figure 7G). It is the opinion of the bronchoscopist (Dr. Samson) that the swelling portrayed in this X-ray is greater than that seen by him through the bronchoscope. Whether or not this is the case, it is reasonable to suppose that the immediate response of an inflamed mucosa to X-ray treatment would be some additional swelling. How long the reaction might last cannot be said, but it is certain in this case that at the time of the lipiodol filling, five weeks after the end of the treatment, there was still swelling of the mucosa. If the original swelling is followed by a shrinkage attributable to the X-ray treatment, then that shrinkage did not take place within the five weeks covered by this observation.

What other effects, beneficial or harmful, there may be from X-ray treatment in this condition cannot be said. In case 5 the X-ray treatment was resorted to because of the failure of all other forms of treatment in this condition and because there was in this case a definite tuberculoma of the bronchus. It was assumed that tuberculoma, being of a somewhat similar pathological structure to a tuberculous lymph node, might respond as tuberculous cervical lymph nodes do to this form of treatment. The tuberculoma was observed bronchoscopically before the treatment was begun and at three and eight months after the treatment was ended. The same observer reported that to the best of his visual memory there was reduction in the size of the tuberculoma on each succeeding examination. On the final examination, it was about one-third of its original size. An ulcer reported in the same case, however, was not reported as in any way changed following the X-ray treatments. The treatments in this case were terminated short

[9] The dosage of each treatment was 350 r. The roentgen therapy and roentgenological diagnostic studies were conducted by the Department of Roentgenology of the University of Michigan Hospital under the late Dr. Preston M. Hickey and his successor Dr. Fred J. Hodges.

of the intended dosage because of the development of a febrile pleural effusion which ran a three months course, and which differed in no way from similar courses in other patients undergoing therapeutic pneumothorax. The symptoms of bronchial obstruction had disappeared before the treatments were begun and returned for a period of only eight days, five months after the X-ray treatments.

The evidence, therefore, of beneficial effect of this form of treatment is rather dubious, and it seems probable that from one experience the treatment should not be employed in those cases showing a highly inflamed and swollen mucosa unless there is found reason to believe that obstructive atelectasis is beneficial in these cases. If that is found to be the case, then X-ray therapy is possibly a means toward that end.

Bronchoscopy: In this report, the possible harm of bronchoscopic examination is purposely emphasized. It is true that most of the instances of possible harm from this examination occurred during our earlier experience with these cases, and in cases in which needless biopsies were taken; nevertheless, they should serve as a warning, particularly to those bronchoscopists who may be asked to examine such patients for the first time.

Even though the examination is done as gently as possible, the mere passage of a stiff metal tube over inflamed mucosa may produce enough additional swelling to occlude a bronchus that was previously patent. In the examination of case 6, the bronchoscopist did not attempt to pass the bronchoscope beyond the narrowing in the left bronchus. It cannot be proved nor disproved that the sudden appearance of an area of atelectasis in the X-ray (figure 7C), taken eighteen days after the examination, was due to the trauma of the bronchoscopy.

Whether or not the bronchoscopy is a factor in the production of atelectasis in our cases, the examination has been followed by definitely harmful reactions in two and by definite benefit in four. The bad results occurred under two circumstances. In case 1, the bronchoscope was passed over a trachea that was already narrowed by oedema and swelling, and this was followed by symptoms of suffocation. In case 2, attempts to remove the obstructing crusts from an ulcer resulted in bleeding and further crusting with greater obstruction. On the other hand, temporary relief of symptoms has followed both a simple diagnostic examination and the removal of obstructing material such as inspissated mucous plugs.

Because of the possibility of harm, we are not recommending bronchos-

copy except in those cases where the diagnosis of ulcerations would affect the treatment to be used, and in those cases in which impending suffocation demands a bronchoscopic attempt at relief. The indication first mentioned is justified because the diagnosis of tracheal or bronchial ulceration may prevent the inauguration of a long, useless and perhaps harmful program of collapse therapy. This indication is limited to that group of patients in whom the indications for collapse are to be found primarily in the persistence of tubercle bacilli in the sputum, but in whom the anatomicopathological indications for collapse therapy are not present in the X-rays. In this group, the source of the tubercle bacilli may be the tracheobronchial ulcers rather than the parenchymal lesion. Inasmuch as collapse of the lung will not affect the bronchial lesions nor the bacilliferous sputum arising from these lesions, diagnostic bronchoscopy should be employed to rule out this source of the tubercle bacilli before collapse therapy is undertaken. Cases 2 and 5 illustrate the futility of collapse in this group. In these two cases bronchoscopic diagnosis of ulcerative tracheobronchitis was not made until after a long series of fruitless collapse measures had been employed. In case 6 bronchoscopy was employed for the specific purpose of determining this point before deciding on collapse therapy.

The two indications for bronchoscopy just given are the only two that we have found to be of any benefit to the patient. It is undoubtedly true that we have seen a very limited sample of patients with ulcerative tracheobronchitis since we have tried to adhere to these indications. The very limitation of the indications for bronchoscopy to this narrow field may have allowed us to see only those patients with the poorest prognosis. It is quite possible that, with a wider application of the bronchoscope for diagnosis, we may have to revise our concept of the complication, its prognostic import and its effect on treatment. By definition, the ulcerative form of tracheobronchitis can be diagnosed only by the bronchoscope, and yet the examination of itself may have played a part in the results we have obtained. It may be that we have been "pulling our plant up by the roots to see how it grows." With our present procedure in examination, there is no way of learning the wholly natural evolution of this form of tuberculosis.

The effect of atelectasis on symptoms: In case 1 we had an opportunity to study the changes in symptoms in a patient with recurrent atelectasis of the right upper lobe undisturbed by collapse therapy, bronchoscopy or any treatment other than bed-rest for a period of nineteen months.

Both the symptoms of bronchial obstruction and the atelectasis were intermittent and recurrent, but we could discover no definite time relation between the two events. No fluoroscopic or roentgenographic examination was made during any of the periods of acute respiratory distress, but the atelectasis was both present and absent during periods of comparative comfort. Though the patient died of suffocation, there was no atelectasis in the right upper lobe at autopsy.

The most prominent and constant symptom of the complication is wheezing which is produced by the passage of air through a narrowed or partially obstructed bronchus. If the obstruction becomes complete and no air passes through the bronchus, and if there are no other areas of narrowing of the airway, the wheezing can no longer take place. The atelectasis is obstructive in nature, and no air passes in or out of the bronchus to the atelectatic lobe or lobes. This fact may explain the results that McConkey and Greenberg (4) reported as due to pneumothorax. If, by giving pneumothorax, these authors shortened the bronchi and thus thickened the mucosa to the point of making the obstruction complete, the collapsed lung would cease to inspire, and the symptom of the obstruction disappear though the obstruction would remain. This may also explain the absence of symptoms in our case 6 after the induction of pneumothorax. These facts would also explain the persistence of wheezing in our cases 2, 3, 4 and 5 after collapse therapy; for, if there were other areas of partial obstruction anywhere in the bronchial tree, or, if the obstruction were not made complete by the degree of collapse obtained, the symptoms of partial obstruction would persist.

The effect of atelectasis on the bronchial and pulmonary lesions: We have but two autopsy observations on the end-result of obstructive atelectasis produced by ulcerative tuberculous tracheobronchitis. In case 1, where no collapse therapy was used, the atelectasis was intermittent for nineteen months, but was absent in all X-ray observations for the nine months preceding death. The X-ray observations pointed to a slow but definite clearing of the involved lobe. At autopsy this lobe contained only apparently healed lesions.

In case 2, total collapse of the lung had been maintained for thirty-eight months before death. The pulmonary parenchyma was practically destroyed, the bronchi were ulcerated and markedly dilated (figure 3). The bronchi were filled with an inspissated gelatinous material that protruded above the cut surface. It is probable that this material

contributed to the suffocative death. Air could not be inspired into the lung after the obstructive atelectasis occurred, so that the accumulation of this material could not be coughed out. As it accumulated, it exuded into the bifurcation and obstructed the airway to the good lung. This mechanism could account for the attacks of dyspnoea and wheezing that had occurred with no relation to the injection or withdrawal of air from the pneumothorax cavity. It seems probable to us that the collapse of this lung had contributed to the fatal result by making the bronchial obstruction more complete and permanent, and by interfering with the effectiveness of cough.

Our other observations on obstructive atelectasis are derived only from the X-rays and the clinical course. In case 2, whose autopsy is reported in the preceding paragraph, the X-rays showed a progressive shrinkage of the collapsed and atelectatic lung (figures 2C & D). In case 5 the X-rays show an even more marked shrinkage of the left lung (figures 6E & F). It can only be surmised that the lung in case 5 was undergoing the same changes that were found in the lung of case 2. In case 2, attempts to reëxpand the lung before death met with failure. In case 5, extremely high negative intrapleural pressures brought about no change in the contour of the atelectatic lung. In this case the greater part of the lung appeared healthy before obstructive atelectasis was produced by collapse. Partial reëxpansion should occur under the negative pressures used, unless some complicating factor is preventing the reexpansion. This factor, of course, might be thickening of the visceral pleura following the pleural effusion. There are good reasons, however, for believing that it is not thickened visceral pleura that is maintaining the lung in this contracted state. For at least six months after the pleural effusion was controlled, the left upper lobe was found capable of reëxpansion. When reëxpanded the visceral pleura did not appear thickened (figure 6D). It is reasonable to assume, therefore, that reexpansion is prevented by obstructive atelectasis, and this in a lobe that appeared free of disease in serial X-rays covering a period of sixteen months before the atelectasis became permanent.

In assessing the effect of atelectasis on the pulmonary and bronchial lesions, it must be remembered that the atelectasis, which follows collapse in this complication, is obstructive; that, in contrast to the collapse produced artificially in treating pulmonary tuberculosis in the absence of this complication, there is no drainage from the infected areas. We have reported observations which seem to point to the fact

that obstructive atelectasis in these cases is harmful rather than beneficial. We do not believe these observations are conclusive on this point. Until it is known whether or not obstructive atelectasis is desirable, we cannot know how to advise patients with this complication—ulcerative tuberculous tracheobronchitis. It has been suggested that many of the procedures used now to treat pulmonary tuberculosis, including collapse therapy, are conducive to obstructive atelectasis.

SUMMARY

The six cases reported represent the significant peculiarities associated with ulcerative tuberculous tracheobronchitis when it complicates pulmonary tuberculosis. While they have been varied, the following symptoms and signs have been common to the group and have served in the recognition of cases with this complication.

Symptoms: (1) Shortness of breath may occur early, before the appearance of other symptoms, and may be brought on by slight exertion; later, acute attacks of dyspnoea, or even orthopnoea, occur and are often associated with asthma-like wheezing.

(2) Wheezing, rattle or palpable rhonchi may be inspiratory, expiratory or both, and are not readily dislodged by cough. They may be generalized over both lung fields or subjectively localized beneath the sternum, to one side of the chest, or even to a small area over a single lobe.

(3) A sense of oppression in the chest is common and is frequently localized to the area of the rhonchi.

(4) Paroxysms of violent coughing are characteristic. Dramatic relief has followed the expectoration of a well-formed bronchial plug, but this is not the rule as the sputum is usually glary and tenacious, and its expectoration after great effort, usually brings only partial relief.

(5) Cyanosis is often present and is usually in excess of that to be expected from the extent of the pulmonary lesion. Cyanosis may be transient during violent paroxysms of coughing, wheezing and dyspnoea, or may be constantly present to a mild degree.

(6) Symptoms frequently are brought on or aggravated by change of posture.

(7) The injection or removal of air in pneumothorax patients with this complication bears no constant relationship to the aggravation or relief of symptoms.

Physical Signs: The physical examination, when done carefully and repeatedly, is significant. We wish to emphasize, as do McConkey and Greenberg, the importance of localized rhonchi. These rhonchi persist following cough and are often palpable directly over the affected bronchus. Coarse râles, rattles and groans often obscure the underlying breath sounds. During unilateral complete obstruction, the breath sounds are absent over the affected lung. Signs of shift of the mediastinum toward the affected side and of elevation of the diaphragm on that side are confirmatory, but their absence is frequent. The physical examination alone will not suffice for a diagnosis, but it may often give the first suggestion and is usually confirmatory. Variability in the findings depend on the location, completeness and constancy of the obstruction. Therefore, repeated physical examinations may be necessary to detect any evidence of the complication and are necessary to follow the frequent changes.

Diagnosis: Any of the signs and symptoms enumerated in the two preceding sections suggest the diagnosis of ulcerative tuberculous tracheobronchitis.

Serial chest X-rays often suggest the diagnosis by the sudden appearance of transient shadows of lobar or lobular atelectasis, and by the suddenness and totality of the collapse of healthy portions of the lung following paralysis of the diaphragm or induction of pneumothorax.

Lipiodol instillation may outline irregularities of the tracheal or bronchial lumen; but the interpretation of these irregularities is uncertain, and their absence does not exclude ulcerations on surfaces not outlined in the silhouette.

The persistence of tubercle bacilli in the sputum in noncavernous minimal pulmonary tuberculosis adequately treated, the presence of tubercle bacilli in the sputum in patients with indefinite X-ray evidence of tuberculosis, and the persistence of tubercle bacilli in the sputum in patients with total collapse of the pulmonary lesion, all suggest that the tubercle bacilli arise from mucosal ulcers.

Visualization of ulcers of the mucosa by bronchoscopy is the only certain method of making the diagnosis. In patients with positive sputum, confirmation of the diagnosis by biopsy is unnecessary and dangerous.

Treatment: Antispasmodics, elimination of common protein allergens, tuberculin therapy, ultraviolet light, croup tents and various cough

mixtures have failed to relieve the symptoms or in any way to alter the course of the disease.

Local applications to the ulcers have not been attempted for three reasons:[10] (1) We have observed that individual ulcers without treatment directed toward the lesion have healed in patients who eventually died as a direct result of mucosal lesions in other parts of the tracheobronchial tree. (2) As brought out in the pathological studies of Bugher, Littig and Culp, the lesions are seldom single; but tend to diffuse involvement of the trachea and bronchi, though the bronchial lesion may be unilateral. (3) The lesions are usually associated with oedema which may be intensified by trauma of the bronchoscopic application.

Medium wave-length roentgen treatments have been administered in two cases with ulcerations. In one, it was followed by reduction in size of a tuberculoma, but by no other change. In another, the treatments were interrupted because of the development of fever and the further production of atelectasis (see Discussion).

Bugher, Littig and Culp present evidence that the bronchial and tracheal ulcerations are secondary disseminations from pulmonary foci. It would therefore be expected that control of the pulmonary lesion would be a prerequisite to control of the tracheal and bronchial lesions. It would also be expected that adequate collapse of the pulmonary focus would be beneficial to secondary infection in the tracheobronchial mucosa, just as collapse of the source of sputum is beneficial to laryngeal tuberculosis. These expectations, however, have not been borne out by our experience. Cases 2 and 5 have been cited to show complete collapse of the diseased lung without influencing the symptoms or fatal outcome in case 2, or without influencing the ulcer or positive sputum in case 5. Bilateral pneumothorax in case 3 failed to prevent the onset of symptoms and failed to influence the behavior of the ulcerative lesions which resulted in a suffocative death. Phrenic paralysis in case 4, similarly, failed to affect the symptoms and failed to affect the positive sputum. We have employed some form of collapse therapy in six patients with ulcerative lesions and have observed no benefit to any of the six.[11]

The complication is occasionally seen in patients with large unilateral

[10] Dilatation of cicatricial stenoses is not considered in this report on the ulcerative form of the complication.

[11] Case 6 has recently been treated by pneumothorax in another institution and is not included in this number. The immediate results are reported as favorable.

cavities, in whom the indications for some form of collapse are imperative. In these, the choice is between two evils as brought out by Eloesser, with whom we agree that the collapse should be risked in spite of the fact that collapse does not yield the results in these cases that it does in cases without the bronchial complication. The fact must be faced that death from the bronchial complication is a possibility with or without collapse, but that death from the pulmonary tuberculosis is even more certain without collapse. The cavernous source of the tubercle bacilli may be closed by collapse; to this extent the collapse is helpful and should be tried.

Another problem is presented in cases 2 and 5 in which there were no imperative anatomical indications for collapse. In one case the anatomical indication was in an extremely small minimal lesion; in the other, the indication was the atelectasis produced by the bronchial lesion but mistaken for pneumonia. In both cases the bronchial lesions were the source of the tubercle bacilli which could not be eliminated by collapse; and in both cases the bronchial lesions formed the major disease picture, while the pulmonary lesion appeared comparatively insignificant and was overshadowed by the effects of bronchial occlusion. In these cases, the collapse serves no useful purpose; and in case 2 it appeared to be actually harmful in that it helped to render cough ineffective. In both cases whole healthy lobes were kept in a constant state of useless collapse; and in case 2 a healthy lobe was converted into a mass of atelectasis and fibrosis. Therefore, when the anatomical indications are not compelling, collapse should not be used in the presence of ulcerative tuberculous tracheobronchitis. This leads to the suggestion that whenever collapse is undertaken primarily to eliminate persisting positive sputum, careful history and physical examination should be directed toward the study of the bronchial complication; and when the clinical suspicion of its presence is aroused, bronchoscopy should be used to confirm the diagnosis before embarking upon prolonged useless and perhaps harmful collapse.

Results: The results in nine cases with proven ulcerations have been as follows:

Dead: Four, three by suffocation. On admission, two were classified as minimal and two as moderately advanced pulmonary tuberculosis. Death occurred from nine to sixteen months after the diagnosis of ulcerative tuberculous tracheobronchitis was established by bronchoscopy. One was treated by unilateral pneumothorax, phrenic paralysis and intra-

pleural pneumonolysis; one had bilateral pneumothorax; two had no collapse therapy.

Living: Five. On admission, two were classified as minimal; two, moderately advanced; and one, far advanced. Two had complete collapse by pneumothorax, one of them had an adjuvant phrenic paralysis and intrapleural pneumonolysis, one had phrenic paralysis. All are still under treatment from six months to two and one-half years after the diagnosis of ulcerative bronchitis was established by bronchoscopy. None are ambulatory.

CONCLUSIONS

Ulcerative tuberculous tracheobronchitis exists as a complication of pulmonary tuberculosis with an unknown incidence.

It forms a possible and probable mechanism for obstructive atelectasis and the likelihood of atelectasis is increased following pulmonary collapse measures.

It is a probable source of tubercle bacilli in the sputum: (1) in patients with little or no roentgen evidence of pulmonary tuberculosis; and (2) in patients with adequate collapse of the lung.

The ulcerations and their symptoms, except under one condition, are not affected by collapse of the lung since the rigid bronchi may be shortened but not collapsed. The exception to this statement is found when collapse produces bronchial obstruction, thereby preventing the passage of air through the stricture and so obliterating the symptoms.

Collapse of the lung may be harmful, but reëxpansion of the lung after collapse in our experience has been either impossible or harmful.

The indications for collapse are affected by this complication as follows: (1) Atelectasis, resulting from the complication, may be mistaken for tuberculous pneumonia and this taken as an indication for collapse. (2) Collapse therapy is not contraindicated when the pulmonary lesion *per se* offers an early threat to life. Diagnostic bronchoscopy does not affect the indications for collapse in this group. (3) Collapse therapy is contraindicated when the chief indication for collapse is the control of sputum containing tubercle bacilli.

Diagnostic bronchoscopy is indicated in group 3 to prevent useless collapse therapy.

In the ulcerative form of tuberculous tracheobronchitis biopsy is harmful and bronchoscopy may be harmful. Therapeutic bronchoscopy is indicated when necessary to relieve impending suffocation. In our

present state of knowledge, bronchoscopy may be justified in many other instances as our only means of study.

A rational program of therapy has not been determined.

Our ideas have been in a constant state of evolution since our first contact with this complication seven years ago; this is to be regarded as a preliminary report.

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BRONCHIECTASIS[1]

An Analysis of Its Causes

PAUL M. ANDRUS

Bronchiectasis is customarily attributed to a weakening of the bronchial wall by infection, together with a dilating force of one kind or another. Considerable uncertainty exists as to the probable nature of this latter factor. A variety of dilating forces have been proposed from time to time, but many of these are not consistent with the physical conditions known to exist within the thorax. All are controversial in terms of their relative importance and frequency of occurrence.

We have therefore attempted a systematic examination of the nature, value and direction of the various intrathoracic physical forces, in an effort to evaluate their relative probabilities as dilating agents. Although the approach is made primarily from the standpoint of physics, it has been necessary in addition to show to what extent the nature and occurrence of these forces agree with the known clinical and pathological characters of the disease.

Professor R. L. Allen of the Department of Physics of the University of Western Ontario has very kindly assisted in the preparation of the manuscript and concurs in the correctness of the physical considerations outlined.

THE DILATING AGENTS

The following is a classification of the agents commonly cited as being capable of causing dilatation of bronchi. The physical mechanism of each of these will be examined in an effort to arrive at their relative probabilities as causative factors in this disease.

CLASSIFICATION OF DILATING AGENTS

I. Ectasia from Within the Bronchi

A. A gas-pressure effect due to (1) the negative pressure of the pleural space; (2) cough; (3) partial bronchial obstruction.

B. The pressure of secretion.

[1] From the Mara Laboratory[2] at the Queen Alexandra Sanatorium, London, Ontario.

[2] Assisted by the National Research Council of Canada.

II. Ectasia from Outside the Bronchi
A. Retraction of fibrous tissue.
B. The normal inspiratory dilatation of the bronchi. (Inspiratory tug of the thoracic walls.)
C. Pulmonary atelectasis.

III. Congenital Bronchiectasis

IV. The Rôle of Infection in Bronchiectasis
A. The replacement-abscess hypothesis.
B. Normal versus abnormal dilating forces.

I. ECTASIA DUE TO FORCES OPERATING WITHIN THE BRONCHI

A. Gas-Pressure Effects

(1) Bronchial Dilatation from Gas Pressure Due to the Negative Pressure of the Pleural Space

Bronchiectasis is frequently explained as being due (when the walls are weakened) to the excess pressure of the intrabronchial gas over the subatmospheric pressure of the contents of the pleural space (1) (3) (4). It is commonly added that the abnormally negative intrapleural pressure that results from atelectasis aggravates this effect (5) (6) (7).

In the case of an aerated lung this is obviously not the case. Under these conditions, the bronchi are neither surrounded by nor exposed to the pressure of the pleural space. They are surrounded by respiratory air chambers in which the pressure during respiration is alternately higher and lower than that within the bronchi. The bronchial walls are therefore not directly exposed to the pressure difference between their contents and that of the pleural space, and in the presence of an aerated lung this obviously cannot constitute an immediate dilating force.

It may be reasoned however that such effects may be transmitted to the bronchi through intervening solid tissues. This entire subject has been examined in detail in a preceding complementary communication (9). In this study it is shown that the difference in pressure between the contents of the lung and that of the pleural space is not so directed as to subject the pulmonary tissues to a corresponding mechanical stress. It is necessary however to refer the reader to the above noted communication for the physical details.

This situation then excludes the negative pressure of the pleural

space, normal or abnormal, as an agent in the production of bronchiectasis.

(2) Bronchial Dilatation from Gas Pressure Due to Cough

Cough is commonly considered to be an important agent in the production of bronchial dilatation (17) (18) (54) (58) (59). Miller (1) in discussing bronchiectasis states, "Compared with the force of hard coughing, such forces as may arise in thoracic traction or in massive collapse of the lungs are insignificant." Boyd (26) on the other hand describes the relationship as "highly problematical" and occasional other dissenting voices are heard (19). Other authors (4) (8) (60) consider that dilatation may result from the deep inspiration which precedes or follows cough rather than from the expulsive phase.

The increased mechanical traction of the lung and thoracic walls upon the bronchi which results from full inspiration is examined in a later section (section IV, *B*). The present section is confined to the study of gas-pressure effects.

Let us examine then the gas-pressure relations during the act of cough. As shown in a previous communication (9), the lung is expanded mechanically by traction from the outward moving thoracic walls. The gas pressure falls in the easily expansible respiratory air chambers, and air flows into them primarily from the relatively rigid bronchial reservoir. During inspiration, then, the gas pressure in the bronchi is higher than in the peribronchial tissues, and this is therefore a possible dilating agent. During expiration the pressure relations are reversed and the bronchi are exposed to a compensatory compressing force.

Whether or not the normal physical stresses to which the bronchi are exposed are customarily sufficient to produce bronchiectasis, will be examined at length in a later section (section IV, *B*). We are here concerned with whether cough produces an *enhancement* of the normal pressure conditions such as to subject the bronchi to an *abnormal* dilating stress.

The inspiration preceding cough is customarily more full and executed at a more rapid rate than is normal inspiration; that is, there is a greater flow of gas without corresponding increase of time. This physical situation would in itself result in a greater than normal gas-pressure difference between the interior and exterior of the bronchi. However, full inspiration is accompanied also by a *dilatation* of the bronchi (10), an effect not sufficient to be readily observable in normal respiration.

A larger conducting channel is thus provided for the increased rate of gas flow. Poiseulle's equation shows that the rate of gas flow in a tube varies as the fourth power of the diameter. For example, if the diameter of a tube is doubled, the gas flow will on this account be increased $2^4 = 16$ times. Thus a given increase in the diameter of a bronchus produces a largely disproportionate increase in its gas conducting capacity. Douglas and Haldane (53) have shown experimentally that the functional capacity of the respiratory air passages may be increased by nearly four times during moderate exercise.

This increased size of the conducting pathways must then compensate in whole or in part for the increased gas flow of deep inspiration. A significantly greater than normal gas-pressure difference between the interior and exterior of the bronchi is thus not shown to result necessarily from the deep inspiration preceding cough. As shown above, the bronchi are subjected to a compensatory compressing pressure during the expiratory phase of cough.

An assumption of an increased dilating stress upon the bronchi as a result of gas pressure during cough is thus apparently not warranted; or if present must be relatively slight and not in proportion to the increased gas flow.

It should be noted that the subjective sensation of "force" and "strain" which arises from cough is due largely to spasmodic contraction of the abdominal and other muscles. It is in this sensation that the above quotation from Miller presumably has its source. From the standpoint of the lung, this muscular stress is utilized to produce expiratory elevation of gas pressure. In a previous study (9) it was shown that this pressure may be so distributed as to cause peripheral pulmonary emphysema. From the aforegoing considerations, however, it is apparent that the greater the pressure, the greater is the compressing effect upon the bronchi. Thus, great as the stress of continuous and hard coughing may be, it is not shown that this stress is so directed as to produce dilatation of bronchi. On the contrary it is so directed as to compress and protect them.

Clinical correlation with cough: From the clinical standpoint, although the disease is by some considered to result from chronic cough (chronic bronchitis) (41) (54) (61), the majority of recent observers do not assign any great frequency to this among the causative agents, but emphasize the pneumonic and pneumonia-producing diseases (2) (3) (4) (5) (14) (19) (21) (25) (42) (43) (58).

We may add our own observations on some two thousand exsoldiers of the district who are pensioned for chronic pulmonary disease which became manifest during the war period of 1914 to 1918. These subjects have been clinically reviewed with radiography when indicated, at two- to three-year intervals over a period in excess of fifteen years. Among these we have not seen an individual with idiopathic chronic bronchitis who developed apparent bronchiectasis over this period, except following an intercurrent pneumonia.

Thus the above conclusions that the physical stresses resulting from cough are not so directed as to produce bronchial dilatation, are in the main confirmed by clinical experience.

(3) Bronchial Dilatation from Gas Pressure Due to Partial Fixed Bronchial Obstruction

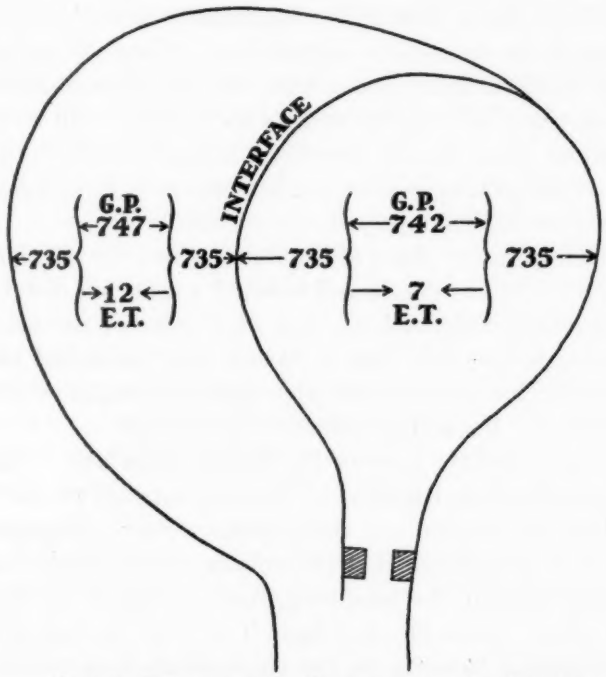
That bronchial obstruction plays an important rôle in bronchiectasis is claimed by practically all authors on the subject. Indeed the gross and rapid dilatation of bronchi distal to an obstructing tumor or foreign body is so impressive as to be convincing of an aetiological relationship (16) (18) (59). To study the expected physical effects upon the bronchi of a partial, fixed bronchial obstruction, it is necessary to examine the effects upon the related section of lung as a whole.

Bronchial obstruction during inspiration: The relative distribution of stresses during the inspiratory phase of respiration in contiguous obstructed and nonobstructed sections of lung is shown schematically in figure I. The arrows indicate the direction in which the forces operate. The values placed outside of the brackets are in each case the algebraic sum of the two directionally opposed forces shown within the brackets, namely the gas pressure (G.P.), and the elastic tension of the lung (E.T.).[3]

Consider first an inspiration commencing from a resting stage sufficient to permit the gas to flow to an equilibrium of pressure throughout the lung. As shown in a former publication (9), the outward movement of the peripulmonary walls results in a dilating traction simultaneously upon all the air chambers throughout the lung. The obstructed and nonobstructed sections of lung are thus subjected to equal initial expansile movements and consequent lowering of gas pressure. However, because of the retarded inflow of gas, the pressure will rise less rapidly

[3] The popular conception of elasticity as "ease of deformity with readiness of recovery of size and shape" is intended throughout the article.

in the obstructed section than in the remainder of the lung, and the surrounding lung will "bulge" into and encroach upon the gas-starved areas. The increased elastic tension resulting from this compensatory over-expansion will however prevent the gas pressure in the obstructed section from being raised to the same level as that of the surrounding lung, as would be the case in nonelastic sacs.



STRESS RELATIONS IN OBSTRUCTED AND NORMAL SECTIONS OF LUNG

FIG. I

Because the obstructed section is under-expanded, its elastic tension must also be subnormal. Since an obstructed section of lung operates at both subnormal gas pressure and subnormal elastic tension during the inspiratory phase of respiration, it would appear that it is specifically protected against mechanical injury at this period. The lower gas pressure however means a greater gas-pressure *difference* for the propulsion of gas past the obstruction. This will partially, but of course not completely, counterbalance the obstructing effect of the same.

The interface between obstructed and nonobstructed sections of lung

has of course no appreciable mechanical rigidity. This surface must therefore at all times promptly adjust its position until the stresses to which its opposite faces are exposed are in equilibrium (735 on each side in figure I).

It should be noted however that a bronchus is not situated as is the stem of a balloon, but is largely invaginated by the functionally related air cells as are the branches of a tree by its leaves. The peribronchial gas pressure is therefore that of the functionally related section of lung and not that of the contiguous normal lung. Since the *rate* of gas flow is slowed down distal to an obstruction, the gas-pressure difference between the interior of a bronchus and its surroundings will be *less* under these conditions than for the bronchi elsewhere. The bronchi of an obstructed section of lung would therefore appear to be still further protected against mechanical injury on this account.

During the inspiratory phase of respiration then, the dilating stresses, both by gas pressure and elastic pull to which a bronchus distal to a fixed partial obstruction is exposed, are less than those of the bronchi elsewhere. We must conclude that a partial fixed bronchial obstruction results in relative mechanical protection against dilatation of the related bronchi during the inspiratory phase of respiration.

This is however not the case for the bronchi elsewhere. The bronchi outside of the obstructed section of lung are exposed to the increased elastic pull of the generalized compensatory over-expansion. If the obstruction is high-grade, and if the volume of the obstructed section is large in proportion to the total lung, this over-stretching may assume important values. On a physical basis it is therefore logical to expect bronchial dilatation to occur in the surrounding lung rather than in the affected bronchus, when a partial fixed obstruction is present.

However, it is generally believed that weakening of the bronchial wall by infection is an important complementary if not a determinative factor in the production of bronchiectasis. Infectious injury, both as a cause and effect, is much more likely to be associated with obstructed bronchi than with those elsewhere in the lung. Unless the bronchi are weakened by infection, this compensatory over-expansion would be expected to involve chiefly the respiratory air chambers rather than the bronchi; that is, to consist of emphysema. As will be enlarged on later, this is in fact the observed effect.

In addition, as will be shown in a later section (see Atelectasis: the distribution of elastic hypertension), the direction of this force is such as

to result for a given chamber, primarily in distortion of form, and not essentially in dilatation.

Bronchial obstruction during expiration: Let us now examine the sequence of events during expiration. As shown in the above noted publication (9), gas is normally expelled from the lung by the simultaneous contraction of the elastic elements throughout, when this is permitted by recession of the thoracic walls. A propelling movement by the thoracic walls is however available as a reserve measure chiefly during cough.

At the commencement of expiration, the lower elastic tension of the obstructed section of lung then implies a subnormal gas-propelling force as compared with the lung elsewhere. Infectious injury, which is apt to be localized because of obstruction, may be expected to lessen still further the elastic recoil of such a section. As expiration proceeds, gas will escape relatively more rapidly from the normal than from the obstructed section of lung. The normal part of the lung may therefore be expected to recede from its position of encroachment on the obstructed section, and eventually a point will be reached at which the gas pressure and elastic tension of the two parts will become equalized.

Thus, from the above considerations it is clear that the force normally utilized in the propulsion of gas past an obstruction in a bronchus is greater during inspiration (greater gas-pressure difference), and is less during expiration (lesser elastic tension), than for the remainder of the lung. From this situation, an accumulation of gas in the obstructed section of lung *in proportion to the size of the bronchial aperture* may then be predicted.

Prior to reaching this point of equilibrium of stresses then, there is a *relative* increase in the volume of gas in the obstructed section in *proportion* to the size of the aperture. The *actual* amount of gas in the obstructed section of lung will however necessarily be subnormal. Subsequent to this point of equilibrium the physical stresses will be the reverse of those previously existing; that is, the section of lung having fixed, partial bronchial obstruction may be over-distended, and operate at a higher gas pressure *as compared with the remainder of the lung at that time.* The excess of gas in the obstructed section will be dissipated during the resting stage which normally follows expiration; or, failing this, the inflow of gas in the ensuing inspiration will be delayed until equilibrium with the rest of the lung is again attained. The over-distention could not be continuous as proposed by MacCallum (8).

The question then arises whether it is possible for this *relative* over-expansion of an obstructed section of lung to become an *actual* over-distention and expose the tissues to mechanical injury. The physical considerations outlined however indicate that, in the presence of a partial fixed bronchial obstruction, the related section of lung at all times contains less than its usual or normal supply of gas. If respiration were suspended for a material period of time at the end of inspiration, a partially obstructed section of lung could acquire its full or normal complement of gas. An actual or absolute over-distention of the section would then be expected to result during the ensuing expiration. Such a suspension of respiration however does not seem to occur other than voluntarily, and its frequency must therefore be low.

An interpretation of over-distention and consequent injury to tissue in a section of lung as a result of a partial, fixed obstruction of the related bronchus, therefore, does not seem to be warranted on a physical basis; rather the reverse is shown to be the case, a section of lung so exposed being specifically protected against injury by over-distention during both the inspiratory and expiratory phases of respiration.

Valvular bronchial obstruction: A number of authors specify or imply that a valvular action may prevent exit of air to a greater extent than inflow, and thus cause bronchial dilatation (2) (4) (5) (8) (15) (16). The term is usually loosely and vaguely used without specific attempt to show a physical basis for a one-way obstruction. Foreign body, tumor, aneurism, kinking, secretion and enlarged lymph nodes as well as functional effects are mentioned as agents which might produce this effect. Such valves may be considered in groups as follows:

(*a*) Aneurism, extrabronchial neoplasm, or enlarged inflammatory lymph nodes, might conceivably from vascular and respiratory movements cause a valvular pressure upon the walls of a large bronchus. Gross over-distention of a lung has on occasion been observed under these conditions. The frequency of such a process must however be very small and is thus a negligible agent as far as bronchiectasis is concerned.

(*b*) Bodies which are moveable within the lumen of the bronchus, such as foreign body, pedunculated tumor, or free secretion. Such a body during inspiration might move to, and be arrested at, positions of normal bronchial narrowing, such as the mouths of smaller tubes or the normal tapering of the bronchi, and be moved away from this position by the expiratory outflow of gas. Such a valve would however limit the in-

flow of air, and favor its exit; that is, would operate to empty and not to over-distend the related section of lung.

(*c*) However, when an *abnormal* fixed partial obstruction exists, such moveable bodies, distally placed, might well exert a valvular action in the opposite direction. Thus in inspiration the flow of gas could move such bodies away from the opening, favoring the inflow of air; while the expiratory flow might lodge a moveable body (such as secretion) in a narrowed aperture, causing greater obstruction during this phase.

Such an over-distention of lung is actually seen when a peanut becomes lodged in a bronchus. It would not be expected however that such a physical state would be sustained for any great length of time. In the presence of an obstruction sufficiently great to arrest the expulsion of secretion, exudation would be accelerated, and complete obstruction and atelectasis would be expected to result soon. Thus, although over-distention of a section of lung is possible under these conditions, the frequency and probable duration of such a process is such that it must be classed among the rarer possible causes of bronchiectasis, and its effects might readily be confused with those of atelectasis.

(*d*) A further type of valve may be proposed to arise from kinking of a bronchus during the respiratory movements, or from buckling of a layer of secretion during the changes in the length of bronchi in respiration. Under these circumstances however, the *mean* size of the bronchial aperture would be the same during inspiration as during expiration. In other words, the valve would operate equally in both directions and therefore have the effect only of a fixed partial obstruction.

The ball-valve proposed by Warner (2), where the lumen is obstructed but the respiratory changes in size of the bronchus continue, is of this same type; that is, the mean size of the aperture would be the same in inspiration as in expiration and the valve would operate equally in both directions.

(*e*) Warner (2) also states that "Central bronchial obstruction has its greatest effect in causing bronchial dilatation during coughing . . ." This would constitute a functional valve. This would be true if respiration were suspended at the end of the inspiration preceding cough, allowing time for the obstructed section of lung to acquire its full quota of air. The expiratory phase of cough would then over-distend this section in proportion to the rest of the lung, because of the impeded outflow of air. Without such suspension of respiration, the resulting

over-expansion is as shown for a fixed bronchial obstruction, *relative* in proportion to the size of the aperture, but not *absolute* in proportion to the normal capacity of the section of lung.

Since such suspension of respiration is not customary, we conclude that specific injury from cough in the presence of partial bronchial obstruction is also not shown to be of significant frequency.

(*f*) Localized muscle spasm as from the irritation of a foreign body or ulcer might conceivably exert a valvular effect. Such an irritable focus would be expected to be particularly stimulated, and the spasm most pronounced, as a result of the stretching effect of the inspiratory movement. Such a valve might therefore be expected to limit the inflow rather than the outflow of air.

(*g*) MacCallum (8) and others (24) propose that the active forces of inspiration as compared with the passive forces of expiration produce a functional expiratory valve in the presence of a fixed partial bronchial obstruction. That this is not the case has been shown at length in a preceding section (I, *A*, (3) Expiration).

We may add that there is no physical reason why such a situation should produce a valvular effect in the presence of obstruction any more than in a normal bronchus.

In conclusion we are unable to determine a physical mechanism by which a valvular retention of gas may other than occasionally be expected to result in over-distention of the related section of lung.

Clinicopathological correlation of partial bronchial obstruction: Since bronchial dilatation is a conspicuous accompaniment of obvious bronchial obstruction (foreign body, tumor, etc.), the above physical conclusions create an apparently anomalous situation. We are faced with the alternative conclusions: first, that something has been overlooked in the physical situation, or second, that the observed dilatation is caused by further associated factors.

Two classes of bronchiectasis may be examined: first, those with obvious obstruction, and second, those in which obstruction is not identified.

When bronchiectasis distal to obstructing tumor or foreign body is seen at autopsy, the condition when recognized during life is identified by the radiographic exhibition of regional atelectasis. This means that the bronchial obstruction has been complete and not partial (12). A narrow channel may conceivably be obstructed either continuously or intermittently by mucous or oedematous mucous membrane, though readily admitting the passage of a metallic sound at autopsy. The

completeness of the obstruction may thus be readily overlooked. It is notable that the types of foreign body especially mentioned and illustrated in textbooks of pathology as causing bronchiectasis are those which swell when wet, and are mechanically adapted to cause adhesion of secretion, namely, beans and twisted string.

Thus bronchiectasis resulting from obvious bronchial obstruction may from the clinicopathological standpoint be at least as well explained on a basis of atelectasis as of partial bronchial obstruction. The physical effects of atelectasis will be enlarged upon in a later section, but we may say in anticipation that the physical stresses resulting from this agent provide the most satisfactory explanation of bronchiectasis of any of the causes currently proposed.

Obvious obstruction as above, of course, explains only a small percentage of cases of bronchiectasis. Because of the conspicuousness of dilatation when bronchial obstruction is gross and obvious, many authors have concluded that lesser degrees of obstruction, as by inspissated exudate, may be a cause of otherwise idiopathic bronchiectasis.

Bronchiolar obstruction may result from pneumonic exudate and produce atelectasis as discussed later (32). It is difficult however to conceive of a mechanism by which a number of large bronchi in both bases may simultaneously undergo an important degree of obstruction, and this is necessary in order to support such a hypothesis. That dilated bronchi are obstructed bronchi is well known (5) (14). When the bronchi and related lung have suspended function, an accumulation and inspissation of secretion may be understood, but this appears to be more logical as an effect than as a cause of dilatation. Again the diseases characterized by chronic purulent expectoration, that is, bronchitis and tuberculosis, in no way provide a reservoir from which the clinical bronchiectatic material specifically appears.

Thus there is nothing in the known clinicopathological characters of bronchiectasis to indicate that the previously noted physical conclusions are not correctly conceived.

From the physical, clinical and pathological considerations involved we therefore conclude: (*a*) That partial bronchial obstruction is not shown to result in physical forces which may produce dilatation of the affected bronchi; and (*b*) that the dilatation observed to occur distal to bronchial obstruction is satisfactorily explained only on a basis of complete obstruction and atelectasis, and not as a result of a partial bronchial obstruction.

These conclusions must not be interpreted as minimizing the possible effects of bronchial obstruction as an agent in the furthering of infectious injury by interference with drainage. They relate only to the mechanical dilating forces concerned.

B. Bronchial Dilatation from the Pressure of Contained Secretion

Although pressure from contained secretion has been cited as a possible cause of bronchial dilatation (17) (18) (52) (54) (55) (65), other recent authors on the subject think that such a force is probably insufficient to produce this effect (2) (8).

As a problem in physics it is sufficient to note at this time that in order to exert a dilating force it would be necessary that the secretion first completely occupy the cross section of the lumen of the bronchus. Such a condition would however necessarily result in atelectasis, and its possible effects be indistinguishable from those of the latter. Further consideration of the subject will therefore be deferred to a later section dealing with the physical effects of pulmonary atelectasis.

II. ECTASIA DUE TO FORCES OPERATING OUTSIDE THE BRONCHI

A. Bronchial Dilatation Due to Contraction of Fibrous Tissue

Retraction of scar tissue is commonly cited as a cause of bronchial dilatation. The majority of authors regard it as an important cause along with other agents (4) (11) (14) (16) (17) (20) (58) (59) (60) (65). Findlay and Graham however assign it "the chief . . . if not the sole" rôle, in the causation of this disease.

The source of these conclusions is presumably the frequent demonstration of conspicuous scar tissue in autopsy material, as well as irregularities and dislocation of adjacent organs as seen in radiographs.

Dissenting voices are, however, raised with increasing frequency as indicated by the following quotations: MacCallum (8), "cannot be a general explanation;" Warner (2), "rarely if ever the primary cause;" Coryllos (1, discussion), "irrational." Other authors describe the development of bronchiectasis in the absence of fibrosis, and with a rapidity which precludes fibrosis as a reasonable cause (3) (5) (21) (32). Hoover (49) doubts the importance of fibrosis as a causative agent because dilatation does not regularly follow when this is present. Kaufmann (18) records that bronchi within contracting lung tissue are "compressed and become obliterated."

Let us examine the problem then from the standpoint of the expected physical effects upon a section of lung, of the development of fibrous tissue. Specifically we have to consider first, whether contraction of fibrous tissue may be so directed as to pull the opposite walls of a bronchus away from each other, that is, to dilate them; and second, whether fibrosis, as is sometimes stated (2), results in an enhancement of the value of the normal respiratory pull upon the walls of the bronchi.

In the first place, if a section of lung undergoes generalized shrinkage in volume as a result of fibrotic contraction, it is apparent that the contained bronchi may participate in the general reduction in size. In any event the shrinkage means that the fibrotic contraction has more than overcome whatever dilating stresses are in operation, and the contained bronchi are therefore specifically protected against dilatation on this account.

If, however, two opposite faces of a continuously fibrotic section of lung are anchored to supports having sufficient rigidity to resist dislocation by the pull of fibrotic shrinkage, the situation may be different. Under these circumstances the walls of the contained bronchi are exposed to the outward pull of the fibrotic shrinkage and dilatation may result from this cause. Continuity of fibrotic tissue and rigidity of anchorage at opposite faces are therefore essential to the production of these conditions. Thus an intervening section of normally elastic lung would destroy the necessary rigidity of anchorage and create a different physical situation as examined later. The diaphragm and the more mobile parts of the bony walls are known from clinical observation to be readily susceptible to inward dislocation. They do not therefore offer anchorage of sufficient rigidity to fulfill the above conditions. Sufficient rigidity of anchorage may however be conceived as possible between the lateral surface of the spine and the relatively rigid and immobile posterolateral thoracic wall. As shown in a former publication (9), the normal forces by which the two layers of the pleura are maintained in position provide more than ample anchorage for the purpose, and it is unnecessary to stipulate the presence of interpleural adhesions. The direction of this axis of anchorage is at right angles to the bronchi at the base and this is the common seat of bronchiectatic disease.

On a physical basis, bronchiectasis of this region may thus be reasonably explained as possible from contraction of fibrous tissue. Whether the necessary continuity of fibrotic tissue commonly occurs across the complete width of the bases is however less clear. The literature of

recent years has emphasized that the most common cause of widespread fibrosis is pulmonary atelectasis (13) (20) (22) (23) (24) (25) (38). However, when a single lobe of a lung becomes atelectatic, it collapses towards its medial attachment at the hilum, and withdraws from the thoracic wall, this space being reoccupied by the elastic tissue of another lobe. Thus, under the conditions most likely to produce a fibrosis of sufficient extent to fulfill the necessary conditions, the continuity is interrupted by withdrawal of the affected lung from its position of anchorage.

We have next to consider whether fibrosis may be expected to alter for better or for worse, the pull exerted upon the bronchi by the normal inspiratory movements. If lung is infiltrated with fibrous strands, the elastic tissue offers increased resistance to expansion: that is, to attain a given increment of expansion a greater tractile force would be necessary than in the case of normal lung; or conversely a given force would produce less expansion. For a given amount of respiratory movement, elastic tissue so splinted would be in the position of a more powerful spring; that is, it would exert greater pull than the normal lung. Providing the splinted elastic were not so over-stretched as to prevent recovery of its original length on release, (that is, the elastic limit were not exceeded), this situation would result in an abnormal dilating stress upon the bronchi. However the recovery of an elastic so splinted would be expected to be also impaired. We know from clinical experience that pulmonary disease very promptly results in localized respiratory lag. Thus this is observable in the region of tuberculous or pneumonic infiltrations known to be of very short duration. It seems very probable that the amount of respiratory excursion at any region is automatically limited by the resistance offered to this movement; that is, that in involuntary respiration the thoracic walls move outward until the usual value of resistance is reached, and that movement is suspended at that point. At any rate we know that the amount of excursion is promptly and materially lessened when pulmonary elasticity is splinted. Such lessening must, at least in part, and possibly wholly, protect the related lung from the increased stress which would otherwise result from fibrotic infiltration.

Again, if a respiratory axis contains both elastic and fibrotic sections of lung, a given respiratory movement would result in greater stretching and tension of the elastic sections than would be the case if the expansion were distributed over a completely elastic axis of the same length.

As before, however, such potential increase in stress can be expected to be more or less completely compensated by lessening of the amplitude of the local respiratory excursion.

From the clinical standpoint, bronchiectasis is customarily of rather acute onset. Progression of the disease is usually by a series of acuities rather than by gradual retrogression. Neither of these considerations fits well with the concept of a frequent origin in fibrosis. As above noted, observers of early pathological material report bronchiectasis in the absence of fibrosis.

Thus, in conclusion: in general it seems probable that pulmonary fibrosis is more apt to protect the bronchi than to subject them to dilatation. Also it is shown that the effects of fibrosis may very readily be confused with those of pulmonary atelectasis. The possibility of bronchial dilatation resulting from pulmonary fibrosis is admitted, but it is not clear on either a physical or a clinicopathological basis that this is probably frequently the case.

B. Bronchial Dilatation Due to the Normal Inspiratory Dilatation of the Bronchi

A physiological dilatation of the bronchi is observable with full inspiration both by bronchoscopy, and by radiography following the instillation of lipiodol (10). Warner (2) (5) points out that this force is so directed as to produce permanent dilatation of bronchi when their constrictor properties are injured as by infection. The consideration is important and has apparently been overlooked by previous contributors. The thoracic wall traction of other authors (18) (49) (58) is however part of the same process (9).

That this physiological dilatation is brought about by traction from the outward moving thoracic walls exerted through the parenchyma of the lung, and not by gas pressure, has been shown in a former publication by this author (9).

Whether this normal force is with any frequency sufficient to produce dilatation of bronchi is however an open question. Since a further school of thought has proposed that bronchiectasis is purely a destructive process and that no mechanical dilating force is necessary, an examination of the relative merits of normal and abnormal dilating forces would seem to be premature, pending a decision as to the probable need of *any* dilating force. Discussion of this situation is therefore deferred to a final section, (section IV).

C. Bronchial Dilatation Due to Pulmonary Atelectasis

The importance of atelectasis as an agent in the production and healing of pulmonary diseases in general, is receiving rapidly increasing attention in the literature. The majority of recent contributors on the subject of bronchiectasis list atelectasis among the important causative agents.

We have, however, seen no satisfactory explanation of the physical conditions which are credited with producing this effect. An examination of the same will therefore be undertaken here.

The physical basis of atelectasis: Atelectasis is identified radiographically by the displacement of organs toward areas of nonaerated lung. This displacement affords us an immediate clue as to the nature of the physical changes which result from atelectasis. The essential physical change that occurs when a portion of lung is collapsed is in effect a removal of a portion of that lung. This of course results from obliteration of some of the air chambers that formerly constituted a portion of its volume. This "lost space" must of course be reoccupied by adjoining structures. Hence the displacement of organs so characteristic of the condition.

This replacement may be effected from intrathoracic or from extrathoracic sources or from both, depending upon the relative resistance to dislocation offered by the parts. The bony walls of the thorax are too rigid to permit of more than mild compensatory collapse. The lost space may however be occupied by an elevation of the diaphragm. If air is admitted into the pleural space, this also may compensate for pulmonary volume lost through atelectatic collapse.

If, however, compensation is not completely effected through these agencies, the only possible alternative is an over-expansion of the remaining pulmonary tissue to occupy the lost space.

The inevitable result of over-expansion of pulmonary tissue is then the production of a state of *elastic hypertension.* This may rise to considerable values and is continuously exerted; and this *increase* in elastic tension represents the *new* intrathoracic force that comes into play when atelectasis is present.

Physical evidence of elastic hypertension with atelectasis: In addition to the anatomical observations above mentioned there are several physical phenomena associated with pulmonary atelectasis which clearly indicate the presence and force of associated elastic hypertension.

The intrapleural pressure. The chief of these is, of course, the abnormally negative pressure in the pleural space.

The normal negative pressure of the pleural space is caused by and is a direct measure of, the elastic recoil of the lung (33). Conspicuous increase in the negativity of this pressure is emphasized by practically all contributors on the subject of atelectasis, (1, discussion by Hedblom) (4) (5) (27) (34) (35) (36) (37) (38). These observers record negativity as high as 100 cm. of water being twenty times that of the normal resting stress.

Abnormally high negative pressures are an every-day event to those administering pneumothorax therapy to the tuberculous. In inducing pneumothorax it is not rare to see the water aspirated from the manometer arm, indicating for the commonly used instruments a negativity of pressure in excess of 50 cm. of water.

The author examined the initial pressures in fifty consecutive cases of successfully attained artificial pneumothorax where dislocation of organs was visible in the original chest radiographs, and a further fifty cases in which such dislocation was not visible. The average figure for the cases in which dislocation of organs was not visible was −4−8 cm. water. The average figure for the cases in which atelectasis might be inferred because of visible dislocation of organs was −8−16 cm. water. An average of double the normal pulmonary tension was thus seen for the group having evidence of possible atelectasis.

Since the normal negative pressure of the pleural space is known to be caused by the elastic tension of the lung, the abnormally negative pleural pressures of atelectasis must indicate a correspondingly increased elastic tension under these conditions.

It should be noted that these values represent, not the initial force resulting from atelectasis, but only the residual force after presumably partial compensation has occurred from outside sources. Again the stress indicated by pneumothorax pressure is a mean value for all directions. As will be shown in a following section, a localization of stresses greatly in excess of the mean value occurs when pneumothorax is not present.

Other physical evidences of elastic hypertension of the lung in the presence of atelectasis: There are other physical phenomena observable when atelectasis is present which are explainable only on a basis of elastic hypertension and not as gas-pressure effects. These are the pendulum movement of the mediastinum; the paradoxical movement of the dia-

phragm; and that very good friend of the pneumotherapeutist, selective collapse. Limitations of space however do not warrant a detailed enlargement of these physical effects at this time, as the existence of elastic hypertension in the presence of atelectasis is abundantly demonstrated by the considerations of the preceding section.

In addition, compensatory over-expansion of the remainder of the lung has been recorded as both a direct pathological and radiographic observation when atelectasis is present (18) (29) (31) (32).

The physical effects on the lung of elastic hypertension: As shown in the preceding sections, the essential change which results when a portion of lung is collapsed is a compensatory over-stretching of the remaining normal lung. Such over-stretching necessarily constitutes an abnormal dilating pull upon all the air chambers involved; that is, both respiratory air sacs and conducting tubes.

The injury which may result from such a stress will depend upon two factors, namely the localization of the force, and the relative ability of the chamber walls to resist it. It is thus first necessary to examine carefully the *distribution* within the thorax, of the elastic hypertension which results when a section of lung is collapsed.

The distribution of elastic hypertension: When a section of lung is collapsed, its dimensions are shortened in all three planes. Compensatory replacement must therefore also be effected in three directions. Elevation of the dome of the diaphragm may replace the shortening in the vertical dimension of the lung, in whole or in part. The anteroposterior and lateral dimensions of the pulmonary cage however remain essentially unchanged. In these planes then the loss in pulmonary dimension can be replaced only by an over-expansion of the remaining lung in these directions.

Over-expansion of lung in the anteroposterior plane results in no readily observable effects. Over-expansion in the lateral plane may however produce conspicuous effects, namely dislocation of mediastinal structures to the affected side. Such displacement is of course due to over-stretching of the shortened elastic, and is not a gas-pressure effect as has been stated (35).

It is important to recognize also that mediastinal shifting does not provide *relief* from the stress arising from atelectatic collapse, but constitutes only an *equalization* of the stress between the two sides.

The quantitative distribution of these stresses is shown schematically in figure II. The cross-lined area represents a collapsed lower lobe.

The position and direction of the maximum abnormal pull is indicated by the arrows marked A, being the situations where shrinkage of the atelectatic section must result in an uncompensated over-expansion of the remaining lung. At the positions marked B, the over-expansion may be at least partly relieved by an upward dislocation of the dome of the diaphragm, and the abnormal stress be thus intermediate or slight

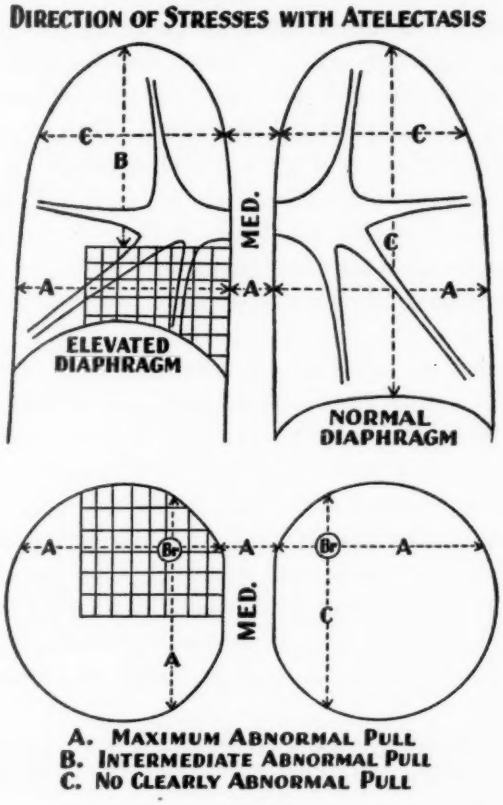


FIG. II

in value. At the positions marked C no direct pull results from the atelectatic shrinkage, although some component of these forces can be presumed to be operative at all positions and directions throughout both lung fields.

The maximum pull resulting from atelectasis is thus seen to occur in all directions in the horizontal plane in the collapsed section of lung. For the lower lobe this force is essentially at right angles to the long axis

of the lower lobe bronchi, and is thus concentrated as to site, and focused as to direction, at the position where bronchial dilatation most commonly occurs. It will be noted that elevation of the dome of the diphragm lessens the dilating stress upon bronchi the main axis of which is horizontal, but affords no relief to the more vertically placed basal bronchi which are in fact the ones most commonly involved.

At the opposite base (when the mediastinum is moveable) and in the lung surrounding the collapsed lobe, the resulting pull at any point is primarily in one direction only. It may thus be expected to result essentially in dislocation and distortion of the bronchi of the part, although having also a lesser dilating effect. Only in the atelectatic section do the deforming forces operate simultaneously in *all* directions, that is, constitute primarily and entirely a dilating stress. Above the level of the collapsed section, no clearly significant new stress arises.

Thus it is seen that atelectasis may result in a concentration and focalization of powerful dilating stresses upon the bronchi of the affected region.

These considerations also indicate that section of the phrenic nerve can only partially relieve the elastic hypertension resulting from atelectasis, and that the relief so attained is not in the direction to protect the basal bronchi. Complete relief in all directions is possible only by the attainment of pneumothorax.

Effects of elastic hypertension on the bronchi: As above mentioned, both respiratory air chambers and conducting tubes are equally exposed to this dilating force when present. Infectious injury of the bronchial wall however may be presumed to be much more likely to be present, both as cause and effect, in the collapsed than in the normal sections of lung.

The bronchi in an atelectatic section of lung are thus specifically and selectively exposed to simultaneous weakening by infection, and a gross abnormal dilating stress. As reviewed in a later section bronchial dilatation is clinically a most conspicuous and constant accompaniment of lobar atelectasis. Here then for the first time is a completely satisfactory physical explanation of bronchial dilatation.

In the case of normal tissues, however, the bulk of the over-expansion would be expected to occur in the respiratory air chambers, because these are microscopically thin-walled and flexible. It is important to recognize however that this over-expansion of the pulmonary parenchyma in no way relieves the tension to which the part is exposed,

unless rupture of a number of air cells occurs. The bronchi may thus continue to be exposed to a very powerful and directionally focused dilating stress. It seems possible that their tonic properties may become exhausted by the continuity of the abnormal pull, and that dilatation may follow in normal bronchi. In fact Kline (42) records that in atelectatic bronchiectasis "Little or no involvement of the muscle and elastic tissue of the bronchial walls may be detected." This may also be the origin of the recorded cases of "dry," that is, uninfected, bronchiectasis, and of those cases that are symptom-free until haemoptysis occurs.

Effects of elastic hypertension on the air cells: Emphysema in bronchiectatic disease: It has already been pointed out that the bulk of the compensatory over-expansion which results when a portion of lung becomes atelectatic must at least primarily be borne by the respiratory air chambers. It is not to be expected however that the pulmonary elastic could for any very great time sustain such an over-extension (8). Thus, unless the atelectasis is "cured" by a reopening of the conducting air channels, or the strain is completely relieved by a compensatory inward dislocation of the peripulmonary walls, the pulmonary elastic must eventually undergo either degeneration of elasticity, or must rupture. Thus, on a physical basis, emphysema would be expected to be the most common injury to result from sustained atelectasis.

There is abundant evidence to indicate that this is actually the case, and the close association of emphysema with bronchiectasis has not in our opinion been accorded the recognition which its frequency and importance warrant. Thus the earliest descriptions of the radiographic appearance of bronchiectasis was that of a "honey-comb" effect (14) (16 and references). Later it was found that less conspicuous ovoid and annular high lights at the bases, gave a good clinical correlation with bronchiectatic disease, and such shadows came to be interpreted as due to dilated bronchi. With the advent of lipiodol, however, it was found that dilated bronchi are only rarely visible without its use. Lipiodol does not customarily enter the ring-like shadows visible in the plain X-ray film and it is concluded that these are of air-cell and not bronchogenous origin; that is, are due to emphysema.

Because of the focalization of stresses as previously outlined, emphysema would be expected to be most pronounced in the lung in the immediate vicinity of atelectasis and bronchiectatic disease. As indicated above, this is distinctly the case. In this coincidence of clinical occur-

rence and anatomical position, we have an entirely satisfactory explanation of the early misinterpretation of emphysematous rings as dilated bronchi. As a matter of fact, the visualization of this type of shadow in association with patchy or lobar airlessness is still the best radiographic index by which the bronchiectatic type of disease is suggested.

FIG. III. For description see text

Again it is common to see conspicuous ring-like shadows in the presence of clinically characteristic bronchiectatic disease, but no bronchial dilatations be demonstrable by the use of lipiodol. Here we may be dealing with the end-results of pulmonary infection and atelectasis, where the bronchi successfully resisted the dilating stress. However, we have seen bronchiectasis at autopsy where a recent apparently well-placed injection of lipiodol did not identify the dilatations, as well as

frequent negative lipiodol findings in entirely characteristic clinical cases; that is, with extensive offensive expectoration and decantation. Boyd (14) emphasizes that dilated bronchi as seen with the bronchoscope are often obstructed by secretion and swelling. Both radiographically and at autopsy gross emphysema may completely overshadow the bronchial dilatation. Figure III is a typical radiograph of this type from an individual having extensive and very offensive expectoration. Microscopically the ring-like shadows were seen to be of emphysematous origin.

The association of emphysema with bronchiectasis and atelectasis is referred to by a number of authors, (8) (13) (16) (18) (48) (56) (58) (64), but as above noted the relationship is not customarily stressed. One of these (Hewlett) states, "Bronchiectasis also arises in connection with emphysema and is merely an extension of that condition," and another (Green), "The causation of bronchiectasis is in great measure analogous to that of emphysema." With these statements, we are in full agreement. Thus although bronchiectasis means only dilatation of bronchi, bronchiectatic disease as it actually occurs is so frequently a combination of bronchial dilatation with severe air-cell dilatation of common origin, that we propose that the term *Pulmonectasis* be used as more accurately descriptive of the basis of this type of disease. Neither the aetiological nor clinical features of what is commonly called bronchiectasis are necessarily dependent upon the presence or otherwise of mere bronchial dilatation. The disease is a chronic septic pulmonitis (1) (43) (43 discussion by Lord) with usually ectasia of both respiratory air chambers and conducting tubes. A nomenclature of the disease which depends upon success or otherwise in demonstrating dilated bronchi is both artificial and misleading.

Atelectatic collapse of bronchial wall from gas pressure: There is, however, in addition to elastic hypertension, a further physical mechanism by which atelectasis may result in bronchial dilatation.

Suppose a bronchus to be imbedded in pneumonic consolidation. If the exudate were to be absorbed from a limited volume of alveoli adjacent to a bronchus while the bronchioles remained plugged, atelectatic collapse of the section would necessarily result. If the rigidity of the surrounding pneumonic consolidation exceeded that of the bronchial wall, atmospheric pressure would push the latter into the "newly created space." If the surrounding consolidation lacks this excess rigidity, the collapse will occur from the pulmonary instead of the bronchial side.

This may well be a cause of saccular bronchiectatic dilatations. We have no means of estimating the probable frequency of such an occurrence but it may well be frequent and important.

Clinicopathological correlation of atelectasis and bronchiectasis: That lobar atelectasis, single or multiple, is with a very high frequency accompanied by gross dilatation of the contained bronchi is generally recognized (2) (3) (6) (27) (29) (30) (31) (32) (50). Such terms as "invariably" (6) and "pathognomonic" (31) appear in the literature in defining this relationship. A major relationship is also described by many authors when atelectasis is recognized though not defined as lobar (4) (7) (16) (18) (24) (28) (42) (51) (56) (60). The clinicopathological correlation of bronchiectasis and atelectasis, when the latter is observed to be present, is thus greatly superior to that of any dilating agent proposed. In fact it is the only relationship which is not highly controversial.

However, although the relationship of lobar atelectasis to bronchiectasis is a very striking one, the former is not identified in any very high percentage of cases. Since we have concluded in the foregoing sections that the various other agents commonly held to be causes of bronchiectasis are unsatisfactory explanations of any important percentage of the same, we are left with a large group of cases which on this basis can be classed only as obscure or idiopathic.

Atelectasis being the only completely satisfactory and undisputed agent to which bronchiectasis is currently attributed, it is legitimate to consider whether this may account for still further cases in this otherwise unexplained group. The following considerations are pertinent to the examination of this question:

(*a*) It is not necessary that atelectasis be lobar in order to result in bronchial dilatation. The physical situation as outlined in this paper indicates that a given volume of pulmonary collapse should be equally effective in producing dilatation, whether it is lobar or patchy in distribution. Patchy atelectasis might however be expected to follow much more easily and frequently pneumonic processes than would a complete lobar collapse.

(*b*) The literature of recent years shows clearly that atelectasis is coming to be recognized as of great frequency and importance in the development and healing of pneumonic diseases of all types. Limitations of space do not warrant a detailed examination of these data here, but the

following references make this point clear (3) (12) (13) (20) (23) (27) (34) (36) (38) (40) (44) (45) (46) (47).

(*c*) Bronchiectasis is generally admitted to have characteristically its clinical origin in the pneumonia-producing and thus atelectasis-producing class of diseases (1, discussion by Coryllos) (2) (3) (4) (5) (14) (15) (19) (21) (25) (42) (43) (58) (59). Strumpell (58) states, "An acute pneumonic origin can be traced in all but a small proportion of cases of bronchiectasis."

(*d*) Patchy airlessness as seen in radiographs of the chest is so constant and conspicuous a feature of the bronchiectatic type of disease as to be one of the chief characters by which this condition is recognized. Muir (60) states, "In adults, saccular bronchiectasis is nearly always associated with a local interstitial pneumonia with condensation and contraction of the lung tissue."

(*e*) The frequent association of conspicuous fibrosis with bronchiectasis in pathological material has led to a general assumption of a causative relationship. However fibrosis is coming to be recognized as most pronounced as a *result* of atelectasis (13) (20) (22) (23) (24) (36). Thus Hennell (20) states, "The marked pulmonary fibrosis which develops after atelectasis occurs, eventually dominates the picture;" and Hamman and Sloan (23) in discussing the pathological anatomy of collapsed lungs state, "The most striking change is the extreme fibrous tissue formation; this occurs in a degree never observed under other conditions." It would therefore seem that the frequent demonstration of fibrosis in the presence of bronchiectasis may be an indicator of the frequent association of atelectasis.

(*f*) Atelectasis may conceivably produce bronchial dilatation but be subsequently dissipated in whole or in part (1, discussion by Coryllos) (3) (32) (36). We have personally observed alternate collapse and re-expansion of atelectatic lobes.

The pneumonia-producing and thus atelectasis-producing class of diseases, which are so intimately associated with the onset of bronchiectasis, are rarely examined radiographically during the acuity. The occurrence of atelectasis at this period is thus not customarily subject to observation.

(*g*) Atelectasis has come to be recognized as a constant and integral part of the development and healing of pulmonary tuberculosis (references as under (*b*)). Dilatation of the regional bronchi would therefore

be expected to be common, as infectious injury is also regularly present. This is described as being the case in many pathological descriptions of tuberculosis (24) (26) (42) (59) (60) (66). Osler (59) states, "It is rare to dissect a lung in the chronic ulcerative form (of P.T.) without finding somewhere a dilated bronchus."

(*h*) Warner (5) states, "We have never observed a definitely bronchiectatic bronchus . . . where the lipiodol appeared to enter the parenchyma . . . ," and Salkin and coworkers (66) in their reports on postmortem bronchography ". . . the alveoli dependent upon these dilated bronchi did not fill with the dye." This is clearly evidence of customary airlessness of the functionally related air chambers.

These considerations individually and collectively may then be fairly interpreted as indicating that the frequency of atelectasis as an antecedent of the bronchiectatic type of disease probably grossly exceeds its customarily recognized occurrence.

When therefore it is considered, first, that atelectasis is much the most powerful and the only universally admitted cause of bronchial dilatation; second, that all other purported causes are trivial, inconstant, controversial or unsatisfactory in nature; third, that bronchiectasis characteristically has its origin in the pneumonia-producing and thus the atelectasis-producing class of diseases; and last, that atelectasis as above is probably much more frequent as an antecedent of bronchiectasis than its commonly observed frequency indicates; we feel justified in concluding that pulmonary atelectasis furnishes much the most logical and probable explanation of the otherwise obscure and idiopathic cases of pulmonectasis.

III. CONGENITAL BRONCHIECTASIS

Congenital malformations of pulmonary air chambers (cystic disease) must of course be admitted as possible, but need not concern us here. A dilatation of originally normal sized bronchi in the prenatal nonfunctioning lung does not seem possible in the absence of air entry.

The causes of immediately postnatal ectasia of bronchi may presumably be the same in kind as in acquired bronchiectasis, namely subnormal strength of the bronchial wall, an abnormal intensity of dilating force, or both. Congenital infection (such as syphilis) may conceivably cause weakening of the bronchial wall, as may mechanical tissue faults, and dilatation result from the early normal inspiratory efforts. Such

a process, if it occurs, may correctly be termed congenital bronchiectasis.

More within our range of knowledge however are the mechanical dilating stresses. Of the various dilating forces outlined in the initial section of this paper, only two appear to be reasonably probable in the new-born infant, namely atelectasis, and partial bronchial obstruction. Atelectasis we know to be common in the new-born and its dilating value as shown, may be very high. We suggest that failure of the bronchi in congenitally collapsed lung to acquire tonicity incident to function, may well be a contributory cause of dilatation. Partial bronchial obstruction in the new-born, though possible, may be presumed to be much less common than atelectasis. Its dilating effects are as shown, not obvious, but doubtful, and easily to be confused with complete obstruction and atelectasis.

As emphasized for the acquired form of the disease, congenital bronchiectasis when interpreted (3) (6) is much more than mere bronchial dilatation. The radiographic picture is a very conspicuous "whorl" effect in a collapsed lung, indicating gross emphysema, that is, torn lung, or pulmonectasis. Thus the best available explanation of "torn lung" in the very young is that the process is the result of pulmonary atelectasis, congenital or acquired.

A further group is met with in congenital "humpbacks," who not infrequently have pulmonectasis, infected or dry. Here we have an abnormal dilating stress identical in kind with that resulting from atelectasis, namely an over-stretching of the lung to fill a chamber which is too large for it. The kyphosis of elderly people develops so slowly that elastic degeneration keeps pace with the over-stretching of the lung and no high-value pull develops at any time. A purely degenerative type of emphysema rather than bronchiectasis results.

Miller (1) proposes that a failure of the terminal buds to expand into alveoli with the initial inspiratory efforts, transfers the stress to the bronchioles which may consequently dilate. On a physical basis there is no reason why the mechanical pull upon a bronchiole should be increased by the failure of the immediately related potential air sacs to expand. However, if such a process occurs *en masse* we have a material degree of atelectasis, and this as above is an entirely satisfactory explanation of bronchiectasis.

Congenital, like acquired bronchiectasis, appears then in the last analysis to resolve itself largely into a matter of pulmonary atelectasis.

IV. THE RÔLE OF INFECTION IN BRONCHIECTASIS

In concluding this analysis of the causes of bronchiectasis, it is necessary to examine the somewhat controversial question as to the relative importance of weakening of the bronchial wall by infection, and of mechanical dilating agents, in the causation of this disease. Many authors both recent and old regard both factors as operative. A further school of thought however proposes that the process is entirely one of destruction, and that it is unnecessary to stipulate mechanical dilating forces. These concepts must be examined in their physical relationships.

A. The Replacement Abscess Hypothesis

It is pointed out by Erb (21) and others (25) (26) that complete destruction of the supporting elements of the bronchial wall may occur. Under these circumstances they state that the disease should be regarded as a replacement abscess rather than an ectasia; also that it is not necessary to postulate a physical dilating force. Such a condition is obviously quite possible. In attempting to estimate its probable frequency the following considerations are pertinent.

The observed pathology: The severe bronchial destruction recorded by the above authors was observed in rapidly fatal pneumonias in infants. This does not constitute *prima facie* evidence of the characters of the process in those in which a lesser intensity of infection permits survival.

Textbooks of pathology describe a wide range of injury to the bronchi up to complete destruction. These sources however frequently record the observation of structurally identifiable bronchial walls and of columnar or ciliated epithelium even in the terminal material upon which they are based, (17) (18) (42) (48) (53) (54) (55) (57) (60) (61). Hyperplastic rather than destructive changes are frequently recorded.

More recently the availability of lobectomy specimens has made possible the study of the anatomical changes in survivors. Under these circumstances the injury is described by Robinson (39) as for the most part an inflammatory reaction in the bronchial wall. Although in the "longer standing" cases varying degrees of injury to the supporting elements of the bronchial wall were seen including complete destruction, it is remarkable that even in this group the epithelium and cilia were for the most part intact. From the standpoint of the present discussion, these observations contain two very significant features. The first is that bronchial dilatation occurred in the inflammatory or predestructive

stage of the infection in those cases in which this stage was observed. Although destructive injury was common in later stages of the disease, it is thus demonstrated that it is possible for this to *follow* rather than *precede* the dilatation. Continued or accelerated injury would in fact be an expected effect of this situation. It follows that destruction of the bronchial walls as seen in late and autopsy material is not satisfactory evidence that this process preceded the dilatation and was a causative agent.

The second significant feature is the frequency with which normal and ciliated epithelium were visualized even where the process was "definitely established." This is of course conclusive evidence that the destructive process in these cases did not pass by continuity of tissue from the lumen to the supporting structures of the bronchial wall. This in turn indicates that bronchiectasis is not necessarily "an excavation in the lung substance starting in a bronchus" as has been stated (25). Neither is the presence of squamous epithelium in itself evidence of destruction and regeneration from residual foci, as metaplastic changes as a result of irritation are characteristic of the bronchial mucous membrane (62).

From the aforegoing considerations we must therefore conclude that destruction of the bronchial wall is not shown on a pathological basis to be a necessary forerunner of bronchiectasis. Although the detailed examination of the factors which go to make up bronchial-wall weakening is not within the scope of this paper, these considerations certainly suggest that nutritional, trophic or tonic disturbances may constitute the "weakening" factor before pure destruction can play a part.

The observed effects of tissue destruction: The effects of a known complete destruction of a section of lung are common knowledge in the case of tuberculosis and lung abscess. Such known destruction of tissue results in the familiar traumatic artefacts or cavities of these diseases. Because the elastic pull of the lung is exerted in all directions upon the margins of such discontinuous foci, the resulting cavities are, in the closed thorax, uniformly spheroidal in form. If the bronchial wall and surrounding lung are completely destroyed as provided by the replacement abscess hypothesis, the resulting artefacts should at least in some measure approach the anatomical and radiographic characters of those of tuberculous disease and lung abscess, since they are exposed to the same dilating stresses. This is in no way the case. Only rarely is a bronchiectatic cavity spheroidal in form or directly visible in the radiograph.

This dissimilarity in the anatomical characters of the two types of cavities suggests that they are not of common origin, that is, that bronchiectasis is not customarily and basically a destructive lung abscess by nature.

Constant existence of dilating forces: It is important to recognize that even if a mechanical dilating force is deemed unnecessary for the production of bronchiectasis, such forces normal or abnormal are nevertheless constantly present (2). Thus, in the course of a destructive process, a point must be reached at which the existing dilating stress, normal or abnormal, exceeds the tensile strength of the bronchial wall, and ectasia will result. In other words it would seem that the normal elastic pull of the lung must produce ectasia, before a condition of pure replacement abscess could be established; that is, even if destruction precedes the enlargement, the process is nevertheless a mechanical dilatation. Since the bronchi are constantly exposed to dilating stresses whether normal or abnormal in degree (2), the proposal of a purely destructive process without mechanical dilating agents would seem to be untenable.

In the light of the pathological clinical and physical considerations of the preceding three sections we are forced to the conclusion that the replacement-abscess hypothesis does not provide an acceptable explanation of bronchiectatic disease.

B. Normal Versus Abnormal Dilating Forces

There remains to consider whether, in the presence of infectious injury to the bronchial wall, dilatation is best explained as being due to the normal elastic pull of the lung as proposed by Warner (2) (5), or whether a dilating stress of abnormal intensity can be customarily expected to be necessary to produce this effect. The former proposal rests upon the undeniable and constant existence of such a normal force, together with the absence of a uniformly identifiable abnormal dilating stress.

Reasons for doubting the efficacy of the normal elastic pull of the lung as a frequent bronchial dilating agent may be expanded as follows:

(*a*) If the normal pull of the lung were a potent factor in the production of bronchial dilatation, this condition would be expected to be a usual or at least a common sequel of pneumonic types of pulmonary infection. This is distinctly not the case.

(*b*) The elastic pull of the lung in ordinary respiration is a relatively

slight force. Only at the end of a forced full inspiration is it sufficient to produce visible enlargement of the normal bronchi (10). Full inspiration customarily proceeds from cough but even here is not usually the maximum possible inspiration. Even when cough is frequent the duration of this peak force is necessarily an extremely small percentage of the twenty-four hours. Unless the muscular and elastic elements of the bronchial wall have suffered almost complete disintegration there is a tremendous preponderance of time during which they may regain their tone. Again, clinically, cough is apparently an effect rather than a cause of bronchiectasis.

(*c*) A further weighty argument against the probability of the normal elastic tension of the lung customarily producing bronchial dilatation, is the fact that a large percentage of cases arises during childhood and infancy. At birth however the lung has no elastic tension, and we are told that an average of seven years and a maximum of fourteen years passes before the adult development of the lung is attained (1). This means that the lung has normally an unusually low elastic tension during the very period in which the development of bronchiectasis is common. A causative relationship is therefore not a logical deduction.

(*d*) The observations of Robinson (39) on lobectomy material show that dilatation regularly precedes destruction of the bronchial wall when the lesion comes under observation at such a stage. The occurrence of dilation at a time when injury to the bronchial wall is of a relatively low order may reasonably be interpreted as indicating that a dilating force of *abnormal* intensity has been operative.

Although this author states, "There was nothing found in our series of cases to indicate that mechanical overstrain such as pleural adhesions, collapsed lung, etc., had played a part," it should be pointed out that this was a highly selected group of cases; that is this group was unusually free from the commonly associated pulmonary infection, otherwise lobectomy would not have been attempted. Thus Smith (43) states, "My experience confirms that of Whittemore that every case of bronchiectasis presents more or less involvement of the parenchyma;" Lord (43, discussion) states, "The pathological process in the lung is ordinarily more important than the bronchial dilatation;" and MacCallum (8) states, "... those acutely produced ... are usually associated with lobular pneumonic patches of consolidation." The absence of visible atelectasis, etc., in this series is therefore not a fair indication of the absence of abnormal dilating forces in the average case of bronchiec-

tasis. Again, as formerly pointed out, atelectasis may be dissipated after causing injury.

(*e*) The high frequency of extensive emphysema in the same section of lung that contains dilated bronchi, as pointed out in a preceding section (II, *C*), is important evidence that the region has been exposed to an expansile stress of supernormal intensity.

The foregoing pathological clinical and physical considerations then, first, indicate serious doubts that the values of the normal ranges of pulmonary tension are sufficient to frequently produce dilatation of bronchi, and second, that there is important evidence that an abnormal intensity of dilating stress is at least frequently operative. The possibility and probability of bronchiectasis resulting from the normal elastic pull of the lung in the presence of unusual severity of infectious injury should be admitted. The balance of evidence however appears to indicate that the major proportion of cases having infectious injury of average severity are the result of a superimposed dilating stress of abnormal intensity. These considerations are in agreement with the most common trend of thought in the literature that both infectious weakening of the bronchial wall and an abnormal mechanical dilating force are customarily determinative agents in the development of this disease.

SUMMARY

1. A detailed examination has been attempted of the nature and value of the various physical forces which are currently held to be causes of acquired bronchiectasis. Correlation has also been made with the recognized clinical and pathological characters of the disease.

2. On these bases it is concluded that the following agents are not shown to exert any clearly significant or frequent dilating stress upon the bronchi. Indeed in some cases they are shown to be constrictive or protective.

(a) The negative pressure of the pleural space
(b) Cough
(c) The pressure of contained secretion
(d) Partial bronchial obstruction
(e) The physiological dilatation of the bronchi
(f) Retraction of scar tissue

3. It is shown that the interpretation of bronchiectasis as being due to some of these causes may result from confusion with the effects of pulmonary atelectasis.

4. It is concluded from the physical considerations involved that the concept of bronchiectasis as being due to destruction without mechanical dilating agents is untenable.

5. The physical nature of the forces arising as a result of pulmonary atelectasis are, as far as we are aware, for the first time completely described. It is shown that the direction, intensity and clinicopathological associations of these forces are such as to provide much the most satisfactory explanation of bronchiectasis, of any of the causes currently proposed. It is therefore concluded that atelectasis is probably a causative agent of high frequency in bronchiectasis, and constitutes the most rational explanation as yet available of the otherwise obscure or idiopathic cases of this disease.

6. The prevailing opinion that both infectious injury to the bronchial wall and an abnormal intensity of mechanical dilating stress are customarily necessary for the production of bronchial dilatation is corroborated by the detailed examination of the physical principles involved.

7. It is pointed out that the bronchiectatic type of disease is not customarily an isolated dilatation of bronchi. It is emphasized that the disease is usually characterized by ectasia of both bronchi and respiratory air sacs of common physical origin. The term *Pulmonectasis* is therefore recommended as more adequately describing the anatomical situation.

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THE SIZE OF THE HEART IN PULMONARY TUBERCULOSIS

A Report of 400 Cases

R. E. PORTER[1] AND WM. H. GORDON[1]

In the minds of many physicians dealing with cardiorespiratory diseases, there appears to be little doubt that in pulmonary tuberculosis the heart is smaller than normal. At least there is a common belief that the cardiac shadow on a teleoroentgenograph taken of an individual with pulmonary tuberculosis is smaller in relation to the transverse diameter of the chest than is found in an individual with no pulmonary disease. This is commonly taught to medical students, and demonstrated in clinics. Certain roentgenologists go so far as to point out cases demonstrating the "drop" heart or "ptotic" heart in the asthenic individual as meaning past, present, or possible future tuberculosis. With these teachings in mind, a search of the literature was made in an effort to determine upon what grounds such assumptions were made, and to ascertain how small a heart must be in relation to the transverse diameter of the chest before it is considered pathological. However, little definite proof was found.

Cardiac measurements were made on 400 cases of pulmonary tuberculosis in an attempt to prove to our own satisfaction that the heart in this disease is smaller than one would normally expect to find in a normal chest of the same size.

REVIEW OF THE LITERATURE

In spite of the commonly accepted belief that the heart in the phthisical individual is smaller than normal, a review of the literature pertaining to the subject reveals conflicting opinions and relatively scant proof to support some of them. A few take it for granted that not infrequently there is a dilatation and hypertrophy of the right ventricle. Boas and Mann (1), in a paper read before the Section of Medicine of the New York Academy of Medicine, quoted the following men: Boh-

[1] United States Public Health Service. Of the United States Marine Hospital, Fort Stanton, New Mexico.

land (a) states that such a hypertrophy is present in chronic tuberculosis and is usually compensatory in nature. Furthermore it is his belief that the enlarged right ventricle, having little reserve, easily becomes insufficient. Krel (b) also mentions that such a hypertrophy is of frequent occurrence. Portal (c), in 1792, on the basis of necropsy studies, believed that the right auricle and ventricle dilate in chronic pulmonary tuberculosis because of obstruction of the pulmonary blood-flow. Laennec, Grissole, Louis, Rokitansky and Rigal on the other hand state that dilatation of the right heart in tuberculosis occurs only exceptionally. Potain (d) noted that the heart of the phthisical patient was usually small and believed that this was due to the cachexia which accompanied the disease. It was his belief that, in those patients in whom the progress of the disease was very slow, large hearts were often found in which the enlargement was probably due to extrapulmonary causes. Regnault (e) found a true or apparent hypertrophy of the heart in the majority of cases of fibroid phthisis. Dilatation of the right heart, particularly of the right auricle, he claimed could be demonstrated quite freqeuntly among living tuberculosis patients by percussion. Hirsch (f) studied the hearts from 120 necropsies in which he found 35 per cent of the cases showed a marked right ventricular hypertrophy. The degree of hypertrophy paralleled the degree of induration of the lungs and the extent of pleural adhesions. He pointed out the interesting fact that in acute ulcerative tuberculosis the heart was small and atrophied. Wideroe (g) found that right ventricular hypertrophy was quite common in pulmonary tuberculosis and furthermore the greater the age of the individual, and the more extensive the lesion, the more pronounced was the hypertrophy. Bret's (h) findings were similar except that in his series of cases he did not find, in all instances, the degree of parallelism between the types of tuberculosis and cardiac size which was present in the series reported by Hirsch and Wideroe.

Boas and Mann (1) presented data which would tend to disprove the above-mentioned statements. In an electrocardiographic study of 97 patients with pulmonary tuberculosis, it was shown that only 29 per cent displayed right ventricular preponderance, 30 per cent showed left ventricular preponderance, and 41 per cent showed no preponderance of either ventricle. Furthermore, they showed that the right ventricular preponderance is not invariably found in any type of tuberculosis. Left ventricular preponderance is not invariably associated with any particular type of tuberculosis, but was found more commonly among

older patients and twice as frequently in women as in men. Anderson (2), in a study of 100 consecutive admissions to a sanatorium for the treatment of tuberculosis, found that they showed very little deviation from normal, from an electrocardiographic point of view. Neither the degree nor the duration of the pulmonary collapse had any definite relationship to the form of the electrocardiogram. Other studies carried out by Simon and Baum (3) showed that in 250 cases of tuberculosis the electrocardiographic findings varied very little from the accepted normal. In this series 10 per cent of the 250 cases showed a right ventricular preponderance.

Hawes (4) makes the following statement: "Much has been written concerning the small size of the heart in tuberculosis. Some are of the opinion that it is the smallness of the heart, either a congenital or an acquired abnormality, with the consequent poor circulation in the lungs and elsewhere that paves the way for the development of tuberculosis later on." He further states that there are undoubtedly a few individuals of the so called "Sthenic Habitus," who possess a small heart and in consequence a poor circulatory apparatus. "Such individuals may come down with tuberculosis." Second, he states "in most instances a small heart in tuberculosis is due to the wasting affect on the heart muscle, just as the leg, arm and shoulder muscles waste away from the same cause." Laennec speaks of the small heart in pulmonary tuberculosis. In 1830 Sir James Clark, of London, is quoted by Hawes as stating, "The state of circulation in tuberculosis is subject to great variety. I think the powers of the heart are commonly under ordinary standard, whilst the frequency of pulse is generally above it and palpitation is not an infrequent symptom. A small feeble heart I consider a strong predisposing cause of consumption." Danzer (5) stated that, "When the cardiothoracic ratio is under 45 per cent, it points in favor of tuberculosis in the presence of suspicious lung findings. The lower the percentage, the greater the presumption." Bremer (6) said that a small heart with two large lungs is an important element in the predisposition of phthisis.

Anderson (2) states, "Most students of tuberculosis will agree, I think, with the statement that there are no definite cardiac signs accompanying the majority of tuberculous cases and that the disease has no specific effect on the heart aside from that produced by any chronic, debilitating malady."

THE SIZE AND SHAPE OF THE HEART

It is a well known fact that the shape of the heart depends to a large degree upon the shape and size of the body frame. In the asthenic individual, the thorax is long and flat and in this type of chest one commonly finds the so called "drop" heart, or Kraus and Wenckebach's *Cor pendulum*. The smallness of the heart in this type of chest may be more apparent than real. This is equally true in the hypersthenic type of chest in which we find the diaphragm pushing the apex of the heart upward and tilting the entire heart in such a manner as to give one the impression of cardiac enlargement. This enlargement is also more apparent than real.

There are other factors which enter into the problem of determining cardiac size and shape. Holmes and Ruggles point out in their textbook of roentengenology that age, height, weight, and sex influence the size and shape of the cardiac shadow. Keeping this in mind one realizes that it is practically impossible for the clinician or roentgenologist to determine whether a heart is "slightly small" or "slightly large" simply from a teleoroentgenogram. Some of the methods that have been suggested as a means of simplifying the problem will be mentioned.

Moritz, in 1902, proposed a complicated system of vertical, longitudinal and transverse diameter measurements in an effort to determine the normal relationship between the diameter of the heart and the diameter of the chest. Other investigators who have contributed to the literature on this subject are Clayton and Merrill (7), Williamson (8), Shattuck (10), Bardeen (9), B. Smith (11), H. E. Smith and Bloedern (12), Danzer (5), Eyster (13), Hodges and Eyster (14), Bainton (15), and probably many others. No time will be spent in discussing the different methods proposed by these men. The method proposed by Hodges and Eyster was the one used in the study of this series.

METHODS

We realize that the formula recommended by these authors was to be used primarily when orthodiagraphic technique was employed for determining the transverse diameter of the heart. We believe that this will detract in part from the value of the paper but we also believe that mathematically the error is too small to be of great importance.

The formula for determining the transverse diameter of the heart is as follows: predicted TD = $0.1094 \times A - 0.1941 \times H + 0.8179 \times$

W-95.8625; when TD = transverse diameter (in mm.); A = age (in years); H = height (in inches) and W = weight (in pounds). This formula was suggested after a study of 80 subjects had been made in which there was no evidence of cardiac pathology. A later article by Eyster (13), in which another 100 patients were added to the original, showed that 3 per cent exceeded the predicted transverse diameter by more than 10 per cent, which means that it is 19 per cent more efficient than assuming an average for all cases.

In their original article the authors pointed out that, of the variables, weight exerted the greatest effect on the transverse diameter. Age was next in importance and height affects the transverse diameter least.

TABLE 1

A tabulated summary showing age distribution and a comparison of the measured transverse diameter (MTD) and the predicted transverse diameter (PTD) of the different age groups

AGE	NUMBER OF CASES	PER CENT	MTD > PTD		MTD < PTD		MTD = PTD	
			Number	Per cent	Number	Per cent	Number	Per cent
years								
18–20	6	1.5	4	66.6	2	33.3		
20–30	176	44	85	48.4	76	43.1	15	8.5
30–40	142	35.3	78	24.6	24	37.8	10	7.7
40–50	50	12.5	26	52	21	42	3	6
50–60	25	6.25	10	40	11	44	4	16
60–67	1	.25						
All ages....	400		203	50.5	165	41.5	32	8

DATA

The present report is the result of a study made of the teleoroentgenograms of 400 patients who had pulmonary tuberculosis. Of this number 54, or 13.5 per cent, are dead. Of the remaining 346, some are still in the hospital under treatment, some were discharged as apparently arrested, while others left the hospital against medical advice. Therefore it is quite possible that more than 54 are now dead but we have no record to show this to be true.

All of the patients were male beneficiaries of the United States Marine Hospital, and had been sent to Fort Stanton for the treatment of pulmonary tuberculosis. The age range was from 18 to 67 years, and age distribution was as follows: from eighteen to twenty, 6 (1.5 per cent); twenty to thirty, 176 (44 per cent); thirty to forty, 142 (35.5 per cent);

forty to fifty, 50 (12.5 per cent); fifty to sixty, 25 (6.25 per cent); sixty to sixty-seven, 1 (.25 per cent).

Essentially all types of pulmonary tuberculosis were represented in this group.

The transverse diameter was measured from the original X-ray film in practically all instances. The predicted diameter was computed on

TABLE 2

A summary showing the age distribution of the deaths and a comparison of the measured transverse diameter (MTD) and the predicted transverse diameter (PTD) of the different age groups

AGE	NUMBER OF DEATHS	PER CENT	MTD > PTD		MTD < PTD		MTD = PTD	
			Number	Per cent	Number	Per cent	Number	Per cent
years								
20–30	30	55.5	14	46.6	12	40	4	13.3
30–40	13	24	9	69.2	3	23	1	7.7
40–50	8	14	3	37.5	5	62.5		
50–60	3	5	1	33.3	1	33.3	1	33.3
All ages....	54		25	46.29	23	42.59	6	11.12

TABLE 3

A group summary of the average age, height, admission weight, normal weight, measured transverse diameter, predicted transverse diameter and predicted transverse diameter on the basis of the normal weight of the various age groups

AGE	AVERAGE AGE	AVERAGE HEIGHT	AVERAGE ADMISSION WEIGHT	AVERAGE WEIGHT NORMAL	AVERAGE MTD	AVERAGE PTD	PTD ON BASIS OF NORMAL WEIGHT
years	*years*	*inches*	*pounds*		*mm.*	*mm.*	
18–20	18.66	69.3	139	146	115	112.4	117.9
20–30	24.4	68.6	141.8	150	116.3	116.7	120.9
30–40	34	68.8	144	155	121.5	118.99	125
40–50	44.3	68.8	144	154	121.6	120	123.4
50–60	55.4	70	143	156	117.9	118.6	124
60–67	67	66	141	160	120	122	122

the basis of admission age, admission weight, and admission height. The normal weight of the patient was also recorded on his admission to the hospital. Therefore the measured cardiac diameter at the time of entrance to the hospital was compared with the predicted diameter using both the admission weight and the patient's normal weight.

After the computation had been made, the cases were grouped according to age, and a survey was made to determine in how many instances

the heart was smaller than the predicted normal, larger than the predicted normal or the same as the predicted normal. The results are shown in table 1.

The deaths were separated from the entire group and a similar tabulation was made (table 2).

A grand average for age, height, admission weight, normal weight, and predicted diameter of the different age groups is recorded in table 3.

REMARKS

In this study, as is often the case in clinical investigation, our aim was to establish proof to a belief, namely that the heart of the individual having pulmonary tuberculosis is smaller than the predicted normal on the basis of weight, height and age. We found, however, that this was not true of this group of four hundred. We do not wish to draw conclusions from our study. We are merely summarizing our findings. Whether or not the altitude of the hospital, which is 6000 feet above sea level, has any influence on the size of the cardiac shadow is a matter for speculation.

SUMMARY

1. A study was made of the teleoroentgenograms of 400 patients having pulmonary tuberculosis.

2. Their ages range from 18 to 67 years.

3. The study included all clinical types of pulmonary tuberculosis.

4. A comparison was made between the measured transverse diameter of the heart and the predicted transverse diameter.

5. Of the 400 cases, 203 (50.5 per cent) had a measured transverse diameter greater than the predicted diameter, 165 (41.5 per cent) had a measured transverse diameter of less than the predicted diameter and 32 (8 per cent) had a measured transverse diameter equal to the predicted diameter.

6. As is shown in table 2, in a study of the X-ray films of the 54 cases that died, there was very little difference noticed as compared with the general average.

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TUBERCULIN ALLERGY PRODUCED BY PARENTERAL BCG VACCINATION[1, 2]

CAMILLE KERESZTURI, HAROLD A. ROSENBERG AND WILLIAM H. PARK

This report of the development of allergy to Old Tuberculin following parenteral BCG vaccination is based upon the study of 41 subcutaneously and 292 intracutaneously vaccinated children. Since different interpretations in reading tuberculin tests are probably responsible for the wide variations reported in the literature on the subject, a definition of our standards is given.

All tests are done by the Mantoux method of intracutaneous injection. The minimum reaction considered positive is one in which the induration is at least 10 mm. in diameter. All reactions smaller than this, and reactions in which erythema alone is present, are called negative. The routine doses of Old Tuberculin on which this study is based are 0.1 and 0.2 mgm. Positive reactions to smaller doses, and negative reactions to larger doses are also considered in our tables. With these doses most reactions measure 10 to 30 mm. in diameter. Occasionally we encounter larger reactions or blistering. Sometimes we use larger doses, ranging from 1 to 100 mgm. Old Tuberculin in testing suspicious reactors. Positive reactions to these large doses of Old Tuberculin are not included in the present tables.

A comparison of allergy following intracutaneous and subcutaneous vaccination is not quite justifiable because of the different doses of vaccine used in the two groups. The use of smaller doses of vaccine for subcutaneous vaccination is essential in order to reduce the number of cold abscesses at the site of inoculation. However, even if dissimilar doses of vaccine were used for the subcutaneous and intracutaneous BCG vaccination, a comparative study is important in evaluating the efficacy of the two methods in producing allergy.

[1] From the Department of Health, New York City.

[2] This study is based on material collected in connection with the BCG investigation by the pediatric staff of the Bureau of Laboratories, New York City. The staff consisted of Dr. C. Kereszturi, Dr. M. I. Levine, Dr. P. Vogel and Dr. H. Rosenberg, pediatricians; Margaret F. Sackett, R.N., Raynie P. Stebbins, R.N., and Gertrude Richardson, R.N., visiting nurses; Agnes Leach, social worker.

From chart 1 it is seen that allergy develops sooner and in relatively more cases in the intracutaneous group than in the subcutaneous group. The chart is self-explanatory.

In the intracutaneous group, 53 cases have been tuberculin tested weekly following vaccination. At the end of the first week following

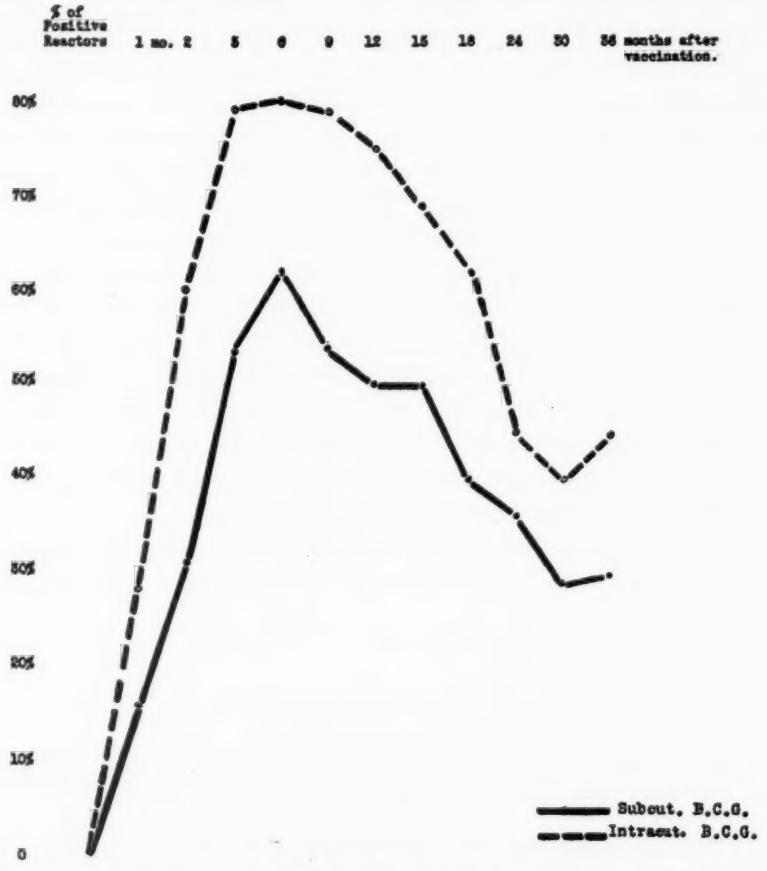

CHART 1. The development of allergy to Old Tuberculin following subcutaneous and intracutaneous BCG vaccination

vaccination, none of the cases have become allergic. At the end of the second week, two cases (4 per cent) reacted positively; at the end of the third week, 8 (15 per cent) and at the end of the fourth week, 15 (28 per cent).

As was previously stated, this report is limited to a study of allergy to

doses of 0.1 and 0.2 mgm. of Old Tuberculin. Wallgren (1), in a study of 33 intracutaneously vaccinated children, found they all developed a positive Mantoux reaction to 1.0 mgm. He reports that hypersensitiveness usually develops in six to seven weeks, and always by the sixteenth week. He advises revaccination if allergy fails to develop by the sixth or seventh week. Parisot and Saleur (2), reporting on 651 infants subcutaneously vaccinated with 0.01 to 0.02 mgm. of BCG, found but 62 per cent positive Mantoux reactions in the group. The dose of Old Tuberculin used is not stated. In 914 subcutaneously vaccinated newborn infants who were given a dose of vaccine comparable to 0.01 of our vaccine, (400,000 bacillli), Cantonnet (3) reported 54 per cent positive Mantoux reactions in one year. Foley and others (4) found 48 per cent of 285 subcutaneously vaccinated children had developed a positive Pirquet. At the seventeenth month following vaccination, the number of positive reactors was reduced to 18 per cent. In a study of a group of parenterally vaccinated children, Domenech (5) found that one-third of the cases became Pirquet positive after vaccination. However, when the group was Mantoux tested with 10 mgm. of Old Tuberculin, every case gave a positive reaction. It has been our experience that the use of doses of tuberculin ranging from 1.0 to 10.0 mgm. for testing increased the number of positive reactions only 10 per cent.

The development of allergy following intracutaneous and subcutaneous BCG vaccination has been studied in relation to the following factors:

(*1*) Dose of vaccine
(*2*) Age of vaccine
(*3*) Age of patient at time of vaccination
(*4*) Local lesion
(*5*) Lymph node reaction
(*6*) Exposure before and after vaccination

The number of cases in the subcutaneous group is very small and therefore the figures of that group will be presented occasionally without comment. However, sufficient cases are available in the intracutaneous group to warrant studying the effect of the factors mentioned above upon the development of allergy.

(*1*) *Dose of vaccine:* As we have previously stated, smaller doses of vaccine are used for subcutaneous than for intracutaneous vaccination. The doses range in the former from .001 to .05 mgm.; in the latter, from

.003 to 0.30 mgm. On several occasions, the dose was divided, and equal parts given in each thigh, represented in table 1 as 2 x 0.15 and 2 x 0.01. One milligram of the bacterial suspension contains 40 million slightly virulent bacilli.

It would appear from these findings in table 1 that a dose of 0.15 mgm. is superior to smaller doses in producing allergy, but larger doses do not increase this advantage. In the small subcutaneous group, the 0.01 dose is superior to smaller doses in producing allergy. Both patients who received larger single doses, 0.03 and 0.05 mgm., developed a positive

TABLE 1

Comparative study of allergy in subcutaneous and intracutaneous BCG vaccination in relation to dose of vaccine

DOSE	NUMBER OF CASES	POSITIVE MANTOUX REACTION
Intracutaneous vaccination		
mgm.		
0.003 to 0.1	33	18 (55%)
0.15	169	142 (84%)
2 × 0.15	24	21 (87%)
0.30	21	16 (76%)
Subcutaneous vaccination		
0.001 to 0.005	21	10 (48%)
0.01	6	5 (83%)
2 × 0.01	5	4 (80%)
0.03		
0.05	2	2 (100%)

Mantoux reaction. However, with these larger doses, the incidence of local cold abscesses is high and therefore they are undesirable.

(*2*) *Age of vaccine:* The bacillary suspension used for vaccination in this study is prepared from culture every ten days. The age of the vaccine consequently ranges from one to ten days. From table 2 it is apparent that the older vaccine is as efficacious in producing allergy as that freshly prepared. The age range of the vaccine is small, and it is problematical whether any difference would be found with vaccines several weeks old. In this respect, Heimbeck (6) found that ten cases who were given 45-day-old vaccine subcutaneously all failed to develop a positive Pirquet reaction.

(*3*) *Age of patient at time of vaccination:* In a group of 251 intracutaneously vaccinated children whose allergy was studied in reference to their age, 238 (95 per cent) were less than one year of age. No difference in the frequency of positive reactors during any period of the first year was

TABLE 2

Comparative study of allergy in intracutaneous BCG vaccination in relation to age of vaccine

AGE	INTRACUTANEOUS	
	Number of cases	Positive Mantoux reaction
days		
0–2	42	36 (85%)
2–4	45	37 (82%)
4–6	62	53 (85%)
6–8	42	31 (74%)
8–10	51	42 (82%)

TABLE 3

Comparative study of allergy in intracutaneous and subcutaneous BCG vaccination in relation to age of patient

AGE	NUMBER OF CASES	POSITIVE MANTOUX REACTION
Intracutaneous vaccination		
months		
0–6	184	150 (82%)
6–12	54	48 (88%)
12–36	13	4 (31%)
Subcutaneous vaccination		
0–6	16	8 (50%)
6–12	11	7 (64%)
12–72	14	8 (57%)

noted (table 3). The age is represented in table 3 in six months periods. However, a more detailed study was also done, considering the age of the children when vaccinated, at monthly intervals, but no difference was found. Only 13 children vaccinated after the first year of life are available for this study, 4 of whom became allergic. We do not feel justified in drawing any conclusions from this small number. In the subcutaneous group, no difference in the frequency of the development of a positive Mantoux reaction was noted at different ages.

(4) *Local lesions:* Local lesions which develop following vaccination with BCG differ according to the method of injection of the vaccine. Following intracutaneous vaccination, a lesion resembling a solitary maculopapular tuberculide developed in 91 per cent of the cases, and became necrotic in 53 per cent. In the subcutaneous group, a deep nodular mass was felt in 61 per cent. The mass enlarged and broke through the skin in 54 per cent.

We may conclude from the data in table 4 that the development of allergy bears a direct relationship to the severity of the local reaction to the vaccine. This is in accord with the report of Foley and others (4). In a group of 285 subcutaneously vaccinated children, they found a

TABLE 4

Comparative study of allergy in intracutaneous and subcutaneous BCG vaccination in relation to local lesions

LOCAL LESION	NUMBER OF CASES	POSITIVE MANTOUX REACTION
Intracutaneous vaccination		
No local lesion	26	11 (42%)
Local lesion—not necrotic	138	107 (78%)
Necrotic local lesion	119	105 (88%)
Subcutaneous vaccination		
No local lesion	16	6 (37%)
Nodular mass—no ulceration	3	1 (33%)
Cold abscess—ulceration	22	17 (77%)

positive Pirquet reaction in 48 per cent. However, among 22 of the group with local nodules, and in 68 who developed cold abscesses, the incidence of a positive Pirquet reaction was 90 per cent.

(5) *Inguinal lymph node reactions:* Following vaccination on the thigh, enlargement of the inguinal lymph nodes was evident to clinical examination in 76 per cent of the intracutaneous and 56 per cent of the subcutaneous cases. The nodes suppurated in 15 per cent of the intracutaneous group, and in 2 per cent of the subcutaneous cases. A survey made recently in our group has revealed that the number of suppurating inguinal nodes following intracutaneous vaccination with 0.15 mgm. BCG is over 25 per cent. The relationship between the development of

allergy and enlargement and suppuration of the inguinal nodes is presented in table 5.

The data in table 5 show very strikingly that, as was noted in the study of local reactions, there is a direct relationship between the severity of the lymph node reaction and the development of allergy.

TABLE 5

Comparative study of allergy in intracutaneous and subcutaneous BCG vaccination in relation to demonstrable alterations in inguinal lymph nodes

LYMPH NODES	INTRACUTANEOUS		SUBCUTANEOUS	
	Number of cases	Positive Mantoux reaction	Number of cases	Positive Mantoux reaction
No nodes	67	37 (55%)	19	8 (42%)
Enlarged nodes	173	143 (83%)	21	13 (62%)
Suppurating nodes	43	43 (100%)	1	1 (100%)

TABLE 6

Comparative study of allergy in intracutaneous and subcutaneous BCG vaccination in relation to exposure

EXPOSURE	INTRACUTANEOUS		SUBCUTANEOUS	
	Number of cases	Positive Mantoux reaction	Number of cases	Positive Mantoux reaction
Exposure within three months prior to vaccination				
No exposure	89	62 (70%)	21	7 (33%)
Exposure to closed tuberculosis case	68	60 (88%)	5	4 (80%)
Exposure to open tuberculosis case	91	77 (85%)	15	12 (80%)
Exposure after vaccination				
No exposure	121	88 (73%)	30	16 (53%)
Exposure to closed tuberculosis case	73	58 (79%)	5	2 (40%)
Exposure to open tuberculosis case	57	50 (88%)	6	5 (83%)

(6) *Exposure to tuberculosis:* We have divided our study of allergy in relation to exposure into two phases: (1) exposure to tuberculosis occurring within three months prior to vaccination; and (2) exposure occurring immediately after vaccination. Since only those children with a negative tuberculin reaction are eligible for vaccination, exposure longer than three months prior to vaccination should theoretically have no effect upon the development of allergy following vaccination.

From table 6, we see that a higher percentage of those children who were exposed to open tuberculosis within three months prior to vaccination developed a positive Mantoux reaction than children not exposed. There are several possible explanations for this unexpected finding. It may be a purely accidental finding; or a number of the children who were exposed to open tuberculosis, and gave a negative tuberculin reaction at the time of vaccination, may have already been naturally infected, and been in the preallergic incubation period of tuberculosis; or many of the children exposed to open tuberculosis before vaccination continued to be exposed after vaccination as well. The greater incidence of allergy in the exposed group may very well be due to the subsequent exposure rather than that which preceded the vaccination.

We would naturally expect exposure following vaccination to affect the incidence of the development of allergy, since some of the children exposed to open tuberculosis may become naturally infected. Aronson and Dannenberg (7), in a study of 70 orally vaccinated infants, found no definite relationship between the incidence of allergy and the type of exposure following vaccination. They report positive tuberculin reactions in 82 per cent of the cases exposed to open tuberculosis, in 93 per cent exposed to closed tuberculosis, and in 75 per cent who were not exposed. Turpin (8), however, found 10 to 20 per cent more positive reactors in a group of orally and parenterally vaccinated children who lived in a tuberculous environment as compared to a vaccinated group in a nontuberculous environment.

The positive tuberculin test produced by BCG vaccination is not a permanent phenomenon. In a considerable percentage of the cases the tuberculin allergy becomes less intensive between six and twelve months after vaccination and gradually becomes negative after twelve months.

The relative number of disappearing positive Mantoux tests in the exposed group is less than in the nonexposed. At the end of thirty months, there are 64 per cent positive reactors in the former group as compared to 40 per cent in the latter. This is probably attributable to the occasional occurrence of natural infection in the exposed group.

All findings thus far reported have comprised results following one vaccination only. Children who were revaccinated were scored only to the time of the second vaccination. In the small group of children who were vaccinated more than once, an interesting finding was noted.

This group comprises only children who failed to develop allergy following the first vaccination.

The findings presented in table 7 indicate that there are apparently some children who cannot be made allergic to Old Tuberculin despite repeated vaccinations with BCG. A satisfactory explanation of this phenomenon cannot be offered.

TABLE 7

Study of allergy following revaccination with BCG in children who did not develop allergy following the first vaccination

METHOD	FOLLOWING 1ST REVACCINATION		FOLLOWING 2ND REVACCINATION		FOLLOWING 3RD REVACCINATION		FOLLOWING 4TH REVACCINATION	
	Number of cases	Positive Mantoux reaction	Number of cases	Positive Mantoux reaction	Number of cases	Positive Mantoux reaction	Number of cases	Positive Mantoux reaction
Intracutaneous.....	26	11 (42%)	10	1 (10%)	2	0 (0%)	1	0 (0%)
Subcutaneous.....	13	3 (23%)	7	1 (14%)		(0%)		(0%)

SUMMARY

1. A report of the development of allergy to Old Tuberculin (0.1 and 0.2 mgm.) in 292 intracutaneously and 41 subcutaneously vaccinated children is presented.

2. Relatively more of the intracutaneous group developed a positive Mantoux reaction than of the subcutaneous group, 80 per cent and 62 per cent respectively.

3. Allergy developed sooner in the intracutaneous than in the subcutaneous cases. The highest incidence of allergy in both groups occurred at the end of the sixth month.

4. The percentage of positive Mantoux reactors at the end of the first year following vaccination was 75 per cent in the intracutaneous group, and 50 per cent in the subcutaneous group; at the end of the second year, 45 per cent and 36 per cent; at the end of the third year, 42 per cent and 30 per cent.

5. In the intracutaneous group, a 0.15 mgm. dose produced a greater incidence of allergy than smaller doses. Larger doses showed no advantage over the 0.15 mgm. dose. In a small dose range used for subcutaneous vaccination, no effect upon the incidence of allergy was noted. Two cases with 0.05 mgm. doses both developed a positive Mantoux reaction, but such doses have the undesirable feature of producing local cold abscesses.

6. The incidence of the development of allergy was not influenced by the age of the patient at the time of vaccination.

7. A direct relationship exists between the incidence of the development of allergy and the severity of the local reaction.

8. A direct relationship exists between the incidence of the development and the severity of the reaction of the regional lymph nodes.

9. The age of the vaccine (1–10 days) does not influence the incidence of positive Mantoux reactors.

10. Relatively more cases exposed to open tuberculosis before vaccination became positive to the Mantoux test than those not exposed.

11. Relatively more cases exposed to open tuberculosis after vaccination became Mantoux positive than those not exposed.

12. There were some children who could not be made allergic to Old Tuberculin despite several vaccinations with BCG.

CONCLUSIONS

1. From the point of view of production of allergy to Old Tuberculin the intracutaneous BCG vaccination is superior to the subcutaneous method.

2. The optimum dose of vaccine for producing allergy in the intracutaneous group is 0.15 mgm.

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TREATMENT OF PULMONARY TUBERCULOSIS WITH GOLD SODIUM THIOSULPHATE[1, 2]

MELVIN TESS

During the past twelve years since Møllgaard (1) published the results of his study of sanocrysin (gold-sodium-thiosulphate) and made claims that the substance has a specifically curative effect in tuberculosis, there have been hundreds of men who have tried the drug on patients and reported their results. However, there is still no uniform opinion as to its place as a therapeutic agent. Most of the writers in foreign countries, but not all by any means, report good results and advocate its continued use, some advocating it along with other treatment, while others rely upon it solely, combined with bed-rest. The writer received the impression that in the United States the predominant opinion is that gold is of little or no use (2) (3). Since there are many who have derived unquestionably good results and since we cannot accurately compare clinical records and statistics of any two writers, because each has his individual method of interpreting results, it appears that work with sanocrysin will continue for some time before universal agreement as to its merits can be determined.

An exhaustive review of the literature for this type of a report is obviously unnecessary. However, it was thought practical to mention some of the fundamental facts that have been observed by others and have been the grounds for much discussion.

Møllgaard believed that sanocrysin, introduced into the bloodstream, permeates tuberculous lesions and there kills many, if not all, offending bacilli. The resulting reactions were interpreted as being due to the liberation of toxins from the bacilli, that is, a tuberculin-like reaction. To offset these reactions, he prepared and administered, at the first sign of a reaction, an antiserum obtained from horses which had been injected with "defatted" formalin-treated bacilli. Some men insist that this antiserum must be given, and that the cause of so many unfavorable

[1] From the Robert Koch Hospital, St. Louis Municipal Tuberculosis Sanitarium, Koch, Missouri.

[2] Read before the Trudeau Club of St. Louis, St. Louis, Missouri, May 7, 1936.

results is due to the fact that many men failed to accept Møllgaard's advice that this serum be used. The general opinion now held is that most of the reactions are symptoms of metallic poisoning and not tuberculin-like shock. Therefore, the serum has been discarded by most clinicians and recourse has been made to smaller and less frequent doses of gold.

According to the present-day opinion, the action of sanocrysin is due to stimulation of the natural defences of the body, producing increased resistance and a stimulating effect on the formation of new connective tissue (4) (5), and not a bactericidal action as Møllgaard proposed. The increased resistance manifests itself by lowered temperature, gain in weight, more favorable blood counts and disappearance of tubercle bacilli from the sputum. The formation of connective tissue is apparently due to stimulation of the reticuloendothelial system and fibrogenetic tissue (6). The contraction of this connective tissue causes the pulling together of cavities and a tendency to fibrosis as shown by X-ray.

Since the action of sanocrysin is one of healing and stimulation of cells entering into the formation of scar tissue, it is quite obvious that when such tissue has already been formed, as in old fibroid cases, little good can be expected. Early cases, those of not more than a year's duration, seem to show the best results. By early cases I am not referring necessarily to those with little involvement, as the Minimal or Moderately Advanced group, but only to those with short duration of the disease. Such early cases that are of the acute or subacute type, or chronic fibrocaseous types in which there are relatively recent discrete tubercles, are the cases that are most often favorably affected. (We did not take this into consideration in the selection of our group as I shall describe later.)

Another large group of patients to whom gold is often given with favorable results, are those in whom collapse measures are used. Cases having pneumothorax, phrenic nerve operations, or thoracoplasties, in whom there occurs a spread of the disease to the better side, often have the new process controlled by gold therapy.

The early workers used large single doses and continued them until a large amount of gold had been given. It was thought by many that a reaction must be produced in the patient in order to get results. It was not uncommon to begin with doses of 500 mgm. and rapidly increase them to 1000 or even 1500 mgm. The total dosage varied between 10 and 30 grams. It did not take long, however, for men to observe that the patients could not tolerate this. Most men now begin with 50 to 100

mgm. and gradually increase to a maximum single dose between 500 and 750 mgm. The sum of all the gold given varies between 6 and 9 grams.

Some of the results often observed are a drop in temperature, rather gradual (over several months duration), and often to normal. This, of course, is absent in a chronic group of patients (such as ours was) because the temperature usually approaches normal. If the dosage is not too large and no gastrointestinal involvement exists, the appetite is often stimulated and the patient gains weight.

As the lesion in the lung forms scar tissue, the sputum decreases markedly in amount. Various writers report the disappearance of tubercle bacilli from the sputum in as high as 50 to 75 per cent.

The blood examination done by many shows a return of the sedimentation rate to normal and a differential count that approaches normal. A substantial increase in monocytes is observed by some men, being interpreted as a stimulation of the reticuloendothelial system (4) (6).

The subjective feeling of well-being is also described by many. It is only natural to expect such an occurrence with the disappearance of toxicity.

The complications encountered are chiefly those of heavy-metal poisoning. Nausea and vomiting are about as frequent as seen in cases receiving salvarsan. The severity and duration varies with the individual. A certain number cannot tolerate gold at all and in them the injections must be decreased or stopped entirely. One must be careful to give the gold on an empty stomach and caution the patient to eat lightly at the following meal. Along with these complaints occur chilly sensations and rise in temperature. Such symptoms rarely persist over twelve to twenty-four hours. Albuminuria of moderate degree may be observed frequently. Treatment need not be stopped for this, but large amounts of albumin require immediate discontinuation of gold. Skin eruptions, usually of a mild degree, occur in individuals sensitive to gold. These may go on to an exfoliative dermatitis and death. It is well to discontinue gold in the presence of a dermatitis, at least for a time, and if return to gold is advisable, do so cautiously with small doses. Icterus caused by liver damage is a rarer complication and accompanied by death in many cases. Stomatitis with ulcerative lesions and salivation may be encountered. Aching in the limbs and joints, usually transient, occurs at times. In fact, all complications seen from heavy metals may be manifested by gold.

An excitation of the lesion with a definite spread by X-ray and physical

examination, high temperature, and general toxicity may be seen. Such cases usually occur in patients receiving large doses.

One cannot tell by any previous symptoms or by any type of lesion present, the group of cases that will react unfavorably. Aside from the group who are extremely ill (who should, of course, be excluded), one may expect complications in any of the patients. It is for this reason that treatment must be started with small doses, and increased according to the patient's tolerance. Some will be found who will not tolerate gold at all.

OUR APPROACH

Since no previous work with gold had been done at Koch Hospital, and since excellent laboratory and X-ray facilities were available, we decided to observe the action of this drug on a number of our patients. Arrangements were made with the Abbott Laboratories, and they generously furnished without cost enough gold-sodium-thiosulphate to carry out our experiment. (Sanocrysin is the trade name given the substance by the original manufacturers. Therefore, we rightly should refer throughout to our substance as gold-sodium-thiosulphate, which is the correct chemical name of the drug; however, since many know this drug better by the term "sanocrysin," we shall often refer to it by this name, or simply "gold.")

At the start of the course of treatment, the entire staff and I myself were more or less prejudiced against gold. If one reviews the literature critically this is only to be expected. With this fact in mind, our series would of necessity comprise those patients in whom the staff considered collapse therapy inadvisable, and those in whom the past treatment had been inadequate to control the disease. All patients had had the disease (with two exceptions) for over one year (some had had it fifteen years). All cases showed bilateral involvement, many with extensive infiltrations and cavitation. The actual average duration of disease of all patients was five and one-half years. I mention this to show that the group chosen was far from ideal; it was not at all the type in which gold was indicated, as recommended by other men; and it was, in fact, a group in which nothing but sanatorium routine could be offered.

Fifty odd cases of this type were selected throughout the hospital and presented at staff meetings. Those in whom some type of collapse measure seemed indicated were withdrawn, leaving forty-eight in all.

Recognizing the necessity of controls, the group was divided approxi-

mately in half. To make an unbiased control of an experiment with tuberculous patients is a most difficult task. However, we followed closely along the method advocated by Sweany (4) for his group of patients. We used the following four methods of control.

(1) A group of patients as nearly like the treated patients as possible, selected with the help of the residents on whose divisions the patients were. The residents and myself reviewed the X-rays, physical examinations, laboratory reports, temperature curves, and in this manner got two groups as comparable as possible. A half-dozen, rather than one man's judgment, made the selection.
(2) Any patient with tuberculosis is apt to do better if he feels that something is being done for him. Therefore, the control group received saline intravenously every time the other group received gold. Six of the control group were told that they received gold along with their antisyphilitic treatment. All who consented received at least some form of injection.
(3) One patient who was selected for treatment refused and was added to the control group.
(4) "Auto-control." By this we mean a comparison of the patient's clinical course before and following treatment. This, of course, supplies the most valuable means of control.

At the end of the course of treatment the patient's X-rays, physical examinations, laboratory reports, temperature, etc. were again reviewed by the various resident physicians, the roentgenologist, and myself. After due consideration of all these factors the patients were classified as to whether they were improved, unchanged, or worse.

If all the cases selected had been in good condition we would have expected good results with or without gold. However, since all the patients were in rather poor condition, we should not attribute a change for the worse entirely to gold if the control group also showed such a change. Therefore, the comparative results, six months after the beginning of the treatment, in the treated and control groups are the basis for commending or condemning gold therapy.

The course of treatment was begun with 5 mgm., then 10, 25, 50, 100, 250, and on up. Two single injections of 500 mgm. were given. Most of the men who stood the treatment well received about 400 mgm. per dose. The women received usually between 250 and 333 mgm. This was continued so that the total dosage for men was set at 6,000 mgm. and for women between 4,000 and 5,000 mgm. Some patients had complications and only small doses could be given, while in others

treatment had to be stopped. When smaller doses were used, that is, up to a dose of 100 mgm., injections were given two to three times a week. With larger doses the interval was increased to one week or ten days.

In view of my sceptical attitude at the beginning of this study I was surprised at the wholly unexpected benefit derived from the treatment.

In estimating the clinical course due consideration was given to subjective symptoms, temperature, weight, physical signs, roentgenological findings, sputum and blood counts. Table 1 summarizes the clinical course of the entire series.

Three in each group died. However, the deaths in the gold group could not be definitely ascribed to the treatment. The first man who died had received only 50 mgm. in four divided doses. This total amount is much less than many workers have given for the first injection.

TABLE 1

Summary of the results in the treated and control groups

	GOLD GROUP	CONTROL GROUP
Number	26	22
Slightly improved	6	2
Definitely improved	9	2
Unchanged	2	7
Slightly worse	4	2
Much worse	2	6
Dead	3	3
Slight toxic effects	4	
Severe toxic effects	4	

He had a large haemorrhage and died several days later. The second man had received only 225 mgm. in seven divided doses. This total amount likewise is less than some authors recommend for the initial dose and it would seem to be too small for a lethal toxic effect. This patient, too, haemorrhaged and died in about one week. The third patient, a white female, had received 1,325 mgm. Her treatments had been discontinued two weeks before her death because she had complained of an aggravation of gastrointestinal distress, which had been present previously. She likewise had a haemorrhage and died two days later. With her haemorrhage she had severe pain in the left chest and became dyspnoeic. It was suspected that she developed either a spontaneous pneumothorax or an atelectasis due to the plugging of a bronchus with blood. Preceding the haemoptysis, this patient had been in a fair

general condition. These three fatal cases had marked bilateral disease with large bilateral cavities.

Our percentage of benefited patients compared very favorably with those of other groups as listed by Sweany (4), especially when we consider the advanced stage of the disease and the poor results of the control series.

The average age of the gold group was 38 years and of the control group 40 years. The average duration of illness for the gold group was 5.7 years, and for the control group 5.4 years. For those definitely improved the average duration of illness was between 3 and 3½ years, substantiating what has been said before, that earlier cases receive the most benefit from this form of treatment.

TABLE 2

Results according to color and sex

	WHITE MALE		WHITE FEMALE		COLORED MALE		COLORED FEMALE	
	Gold group	Control group	Gold group	Control group	Gold group	Control group	Gold group	Control group
Numbers	12	11	8	6	3	2	3	3
Slightly improved	3	0	1	2	1	0	1	0
Definitely improved	4	2	1	0	2	0	2	0
Unchanged	2	4	0	2	0	0	0	1
Slightly worse	1	2	3	0	0	0	0	0
Much worse	0	1	2	1	0	2	0	2
Dead	2	2	1	1	0	0	0	0

Table 2 shows the classification of results according to color and sex.

The white female in the control group who died had been chosen as the control for the treated white female who died; the same was true for one "pair" of white males who died; indicating that the arrangement of each group was as much alike as possible.

The results in the colored group are directly opposed to the results published by Broch (7) who found that gold had little effect upon the progression of acute exudative tuberculosis in the Negro.

Table 3 shows results based on X-ray findings and subjective symptoms.

Table 4 shows the observations on the sputum, regarding its bacillary content and its amount. All patients had 5 sputum specimens examined by concentration (antiformin) at completion of treatment. The three patients in the gold group whose sputum became negative, were negative

for the first time during their treatment, while the two patients in the control group had had negative sputum at different times previously.

The striking observation regarding sputum was the decrease in amount found in the gold group. This was marked, varying from one ounce to 16 ounces in some patients.

TABLE 3

Roentgenological results

	GOLD GROUP	CONTROL GROUP
Improved	9	2
Unchanged	15	12
Worse	2	8
Subjective symptoms		
Improved	12	6
Unchanged	4	3
Worse	10	13

TABLE 4

Observations on sputum

	GOLD GROUP	CONTROL GROUP
Sputum positive before—positive after	22	17
Sputum positive before—negative after	3	2
Sputum negative before—negative after	1	3
Sputum negative before—positive after	0	0
Amount of sputum decreased	12	4
Amount of sputum unchanged	10	13
Amount of sputum increased	4	5

TABLE 5

Haematological picture

	GOLD GROUP	CONTROL GROUP
Less toxic	9	5
More toxic	7	6
Unchanged	10	11

Table 5 summarizes the haematological findings, based on Schilling's differential count. "More toxic" indicates shift to the left, with a decrease in lymphocytes. By "less toxic" we mean a shift to the right and an increase of lymphocytes. Most of the cases chosen were not

acutely ill, but had had their disease a long time (average 5.5 years) and their acute symptoms and toxic haematological manifestations had subsided before the treatment. In table 6 the complications are listed. In three patients the gastrointestinal symptoms became so disturbing that treatment had to be discontinued. Mild nausea and vomiting occurred about as frequently as in cases receiving salvarsan; and these milder symptoms are not included in table 6.

In two patients the dermatitis was severe, covering parts of the extremities, the axillae, the chest and back. Treatment had to be stopped in these cases, and saline, glucose and sodium-thiosulphate were given intravenously twice daily for ten days. The eruptions finally cleared in each patient. The third patient developed a slight eruption on the neck and chin, which cleared when treatments were discontinued.

TABLE 6

Complications

	NUMBER OF CASES
Gastrointestinal distress	4
Treatment stopped because of gastrointestinal distress	3
Dermatitis	3
Albuminuria	2
Stomatitis	1
Increased dyspnoea	1
Neuritis (?)	1
Spontaneous pneumothorax	1
Severe chill (due to saline)	6

One patient developed a questionable stomatitis, with some signs of ulceration. She never had salivation or metallic markings on the gums. The dentist thought that most of the ulceration might be caused by her poor teeth.

One patient with a great deal of scarring and fibrosis, had an increase in dyspnoea. This was presumably caused by the deposition of scar tissue and the patient will probably suffer from this complaint to a greater degree, as he continues to control his disease.

One of the patients who had had a skin eruption caused by gold, also developed what we diagnosed as neuritis. After her dermatitis began to clear, she complained of pains in all extremities, usually of a dull character, but sufficient to keep her awake at nights. Various sedatives were given and infra-red rays were applied to the extremities. The pain and discomfort is gradually disappearing under this simple treatment.

Six patients in the gold group suffered a severe chill on one occasion. However, it so happened that three control patients reacted in the same way on the same day. The cause was finally traced to a contamination in the saline used.

Only two of our patients developed albuminuria who had not had it previously. This is an unusually low figure, for most men report this condition occurring in one-half or more of their patients. Smaller dosage and longer intervals between treatments will allow more complete elimination through the kidneys, and prevent an accumulation which might cause damage to the kidneys. McCluskey and Eichelberger found that most of the gold was excreted through the kidneys in one to three days, but that some could still be found in the urine 100 to 130 days after injection (8).

SUMMARY AND CONCLUSIONS

I believe there is a very small group of tuberculous patients, probably one or two per cent, in whom gold is indicated. This group consists of patients with bilateral involvement in whom collapse therapy is not indicated. This group would consist of patients with recent involvement, not over one to two years' duration, in whom the disease is acute or subacute. Such a group might be benefited by gold through the drug's property of stimulating scar-tissue formation.

Many other gold preparations are on the market, some older, some newer than gold-sodium-thiosulphate. The amount of gold in these compounds varies greatly; gold-sodium-thiosulphate, being among the stronger in this respect, contains 37.4 per cent gold. It is probable that one of the weaker gold compounds, or some other compound having the same connective-tissue stimulating effect, will come into use. Some drug of this nature that would produce the same effect, but cause fewer complications, would indeed be welcome.

In future treatments I would reduce the dosage considerably, and make 250 mgm. the maximum single dose and 3,000 mgm. the total dose. If more were needed, I would repeat the course. We found that our serious complications did not begin until we gave above 250 mgm. and that the severity of these complications increased as the dosage was increased.

Because of the differences in results published, any attempt to popularize sanocrysin therapy among the general practitioners would be disastrous. Only the men thoroughly acquainted with the treatment of pulmonary tuberculosis should use this drug, and then it would seem

best that treatment be given in a hospital where all necessary material for following the patient is available.

What recommendations for or against gold can be given on the basis of our experience? I suspect that I have not improved the opinion held for the use of gold in pulmonary tuberculosis among many of my readers. It appears that the results obtained in our series, as shown by the data presented, were, on the whole, fairly encouraging. However, these results were obtained in a small series and also sufficient time has not elapsed to tell whether continued benefit will be derived or whether those benefited will return to their original condition. I shall not hesitate to use gold in the future, subject, of course, to the limitations just mentioned.

EDITORIAL NOTE: Due to the demands upon our space, it was necessary to delete, with the author's permission, the detailed case histories and an elaborate bibliography that formed part of this paper.

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PNEUMOPERITONEUM IN TREATMENT OF PULMONARY TUBERCULOSIS

A Preliminary Report[1, 2]

HAROLD GUYON TRIMBLE[3] AND BUFORD H. WARDRIP[4]

Rapid strides have been made in the treatment of pulmonary tuberculosis during recent years. In conjunction with bed-rest, various lung splinting procedures, used singly and in combinations, have done much to effect rest and promote healing of the affected lung areas. We are familiar with the marked value of such procedures as pneumothorax, oleothorax, phrenic nerve paralysis, apicolysis, intrapleural pneumonolysis, and thoracoplasty when they are used in well selected cases.

However, with all of these measures at our disposal there is still a large group of patients for whom we have had little to offer in the way of an active approach to their therapeutic problem. This group is made up of persons with fairly extensive bilateral pulmonary disease on whom a pneumothorax cannot be established because of adhesions and who cannot well tolerate, either because of age, debility, or for some other reason, any of the more drastic types of collapse therapy.

There is still another group made up of individuals who have had a phrenic nerve paralysis, but who have obtained an inadequate rise of the paralyzed hemidiaphragm. We feel that these individuals would profit by a more adequate rise and splinting of this leaf of the diaphragm.

Probably we have all noted pregnant tuberculous women, who, during the latter months of gestation, have showed a very definite improvement in their pulmonary lesions, only to have these lesions become very much worse following delivery. This observation frequently occasioned comment during staff rounds and there was considerable speculation as to whether the good effect noted during the latter months of pregnancy was the result of hormonal changes, or whether it was from the mechan-

[1] Presented at the annual meeting of the California Tuberculosis Association, Sacramento, California, April 3, 1936.

[2] Presented in part at a session of the Clinical Section at the thirty-third annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

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ical effect of elevating and splinting the diaphragm. In June, 1934, after reading an article by Dr. Andrew L. Banyai in which he reported a series of 100 cases of pneumoperitoneum which had been used for various pathological conditions, we decided to try to reproduce the mechanical effect of pregnancy by the use of pneumoperitoneum. With the exception of a report of two cases during the previous year by Dr. Ludwig Vadja, practically nothing else was found in the literature regarding the use of pneumoperitoneum in the treatment of pulmonary disease, although pneumoperitoneum and oxyperitoneum have been used for many years in the treatment of intestinal and peritoneal tuberculosis. Pneumoperitoneum was used as a diagnostic measure as early as 1902.

Since starting this work with pneumoperitoneum we have used the procedure in about eighty cases. Statistically our results are not remarkable because it has been employed in instances where, for the most part, there was practically nothing else to offer in the way of active therapy. Frequently the patients were almost moribund before they were seen. On the other hand, some very interesting results have been obtained and we have come to feel that the procedure has a place of therapeutic importance in the treatment of certain types of pulmonary tuberculosis.

As mentioned, the pregnant tuberculous woman suggested to us the possible value of the procedure. Dr. Burgess Gordon of Philadelphia has also tried to reproduce the mechanical effects of pregnancy by a different method, namely by the use of a tailored, snugly fitting abdominal binder. By this means he was able to increase the intraäbdominal pressure and thereby cause some elevation and splinting of the diaphragm. The amount of elevation of the diaphragm even during the latter months of pregnancy may be only from 2 to 3 cm., but it is apparently sufficient to be of benefit to pulmonary lesions. If the amount of elevation caused by pregnancy is of value, we can be quite certain that the amount obtained by the use of pneumoperitoneum will also be helpful because as much as two or three times this amount is obtained by the procedure.

The greatest degree of collapse has been obtained by the use of pneumoperitoneum in conjunction with phrenic nerve paralysis. With the addition of subphrenic pressure by pneumoperitoneum, the paralyzed leaf of the diaphragm may rise sufficiently to reduce the volume of the lung to as little as one-third of its original volume. Usually the amount of elevation obtained by this combination is about double that obtained by the use of the phrenic nerve procedure alone.

When a satisfactory pneumoperitoneum is established, there is almost always some limitation of diaphragmatic motion with normal breathing (it may be increased by forced breathing) and often the diaphragm is almost completely splinted. The amount of diaphragmatic rise varies with the individual, but a rise to as high as the third interspace anteriorly on each side has been noted from pneumoperitoneum alone. (See case 4.) We were interested to note that the elevation of the diaphragm was a little greater with the patient in the upright position; also, that if the patient was on one side constantly, the uppermost hemidiaphragm was more affected. Consequently, when pneumoperitoneum is used in conjunction with phrenic nerve paralysis, the patient is kept upon his good side. This, of course, is contrary to the procedure when a patient is placed at postural rest or upon a bolster.

An abdominal binder used in conjunction with pneumoperitoneum has in our experience not caused any greater elevation of the diaphragm with the patient either upright or recumbent, as noted by comparison of X-ray films taken with or without the binder.

The technique might be briefly described by saying that it is very similar to giving pneumothorax refills. Although any point of the anterior abdominal wall may be used as a puncture site, there is definite advantage to a standardized procedure. We have used the following: The patient is placed in a reverse Trendelenburg position. This position is very effective in localizing the abdominal air beneath the puncture site, and as a result, a fluctuating manometer reading is usually obtained almost as soon as air is first introduced. The site chosen for puncture has been just lateral to the left *rectus abdominis* and immediately below the costal margin. This area has the advantage of not overlying any particularly vulnerable viscera and the proximity to the ribs permits the skin to offer some resistance to the needle rather than being pushed in front of it. This latter fact is especially welcome when the abdominal wall is flaccid, such as one is apt to find in a thin multiparous woman.

The site is well anaesthetized by an injection of 3 cc. to 5 cc. of one per cent procaine down to the peritoneum. An ordinary pneumothorax needle (2-inch, no. 19 gauge, short bevel) is used for the introduction of air and the procedure is identical with that used for pneumothorax. With the initial fill an oscillation of the manometer may not be obtained, but one can determine when the needle has entered the peritoneal cavity by the lack of tissue resistance in front of it and the ease with which the air flows through the needle. Following the initial in-

jection of air there may be some discomfort and shoulder pain for a few days, but if the pain is severe it can be relieved by elevating the foot of the bed which removes the air from the lower surface of the diaphragm. After pneumoperitoneum is established, the manometer readings are almost always positive and may go as high as plus 7 cm., plus 5 cm. (water manomenter) or more. The oscillations of the manometer are narrow as compared to those encountered with pneumothorax, and are paradoxical. The amount of air given should be comparatively small with the first few refills to avoid undue discomfort. Thereafter the amounts of the refills vary from 200 to 500 cc. twice a week, or 500 to 1000 cc. once a week. This, of course, varies with the rate at which the air is absorbed. Because of a relatively large area of peritoneal surface, the air from the peritoneal cavity is absorbed more rapidly than from the pleural space.

As with pneumothorax, complications can and do arise, though in

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PLATE 1

Fig. 1. Normal chest at eight months gestation. Dotted lines indicate level of diaphragm before pregnancy.

Fig. 2. Normal chest of patient who was examined as a tuberculosis contact.

Fig. 3. Chest of same individual who subsequently developed tuberculous enteritis and peritonitis with resulting tympanitis. Film illustrates marked elevation of the diaphragm resulting from intraäbdominal pressure. Dotted lines indicate original level.

Case 1. J. P., age 33. Italian housewife.

Fig. 4. August 1, 1934. Patient first seen at this time with extensive bilateral lesions. A right artificial pneumothorax started.

Fig. 5. September 14, 1934. Selective collapse of right lung by pneumothorax. Left pneumothorax attempted but unsuccessful because of adhesions. Pneumoperitoneum started in December, 1934, to splint the left lung.

Fig. 6. February 11, 1936. Pneumothorax and pneumoperitoneum effective in controlling lesion in right lung. Pneumoperitoneum has resulted in marked elevation and splinting of both leaves of the diaphragm. There has been much clearing of the left lung field. Sputum is diminished, though still positive, and patient has shown much clinical improvement.

Case 2. Wm. J. E., age 47. Irish-American salesman. Had pleurisy in 1932. Onset of symptoms of present illness in October, 1935. First seen in January, 1936.

Fig. 7. December 30, 1935. Acute exudative lesion in upper portion of the left lung. Sputum positive. Attempts to establish a left artificial pneumothorax unsuccessful.

Fig. 8. February 24, 1936. Showing elevation of the left hemidiaphragm following temporary paralysis of left hemidiaphragm done on February 14, 1936.

Fig. 9. March 13, 1936. To augment rise of the left hemidiaphragm a pneumoperitoneum was started February 24, 1936. The patient has been kept on his right side to localize air beneath the left leaf of diaphragm. Pneumoperitoneum has almost doubled the degree of elevation of the left hemidiaphragm. Note clearing of the left lung field.

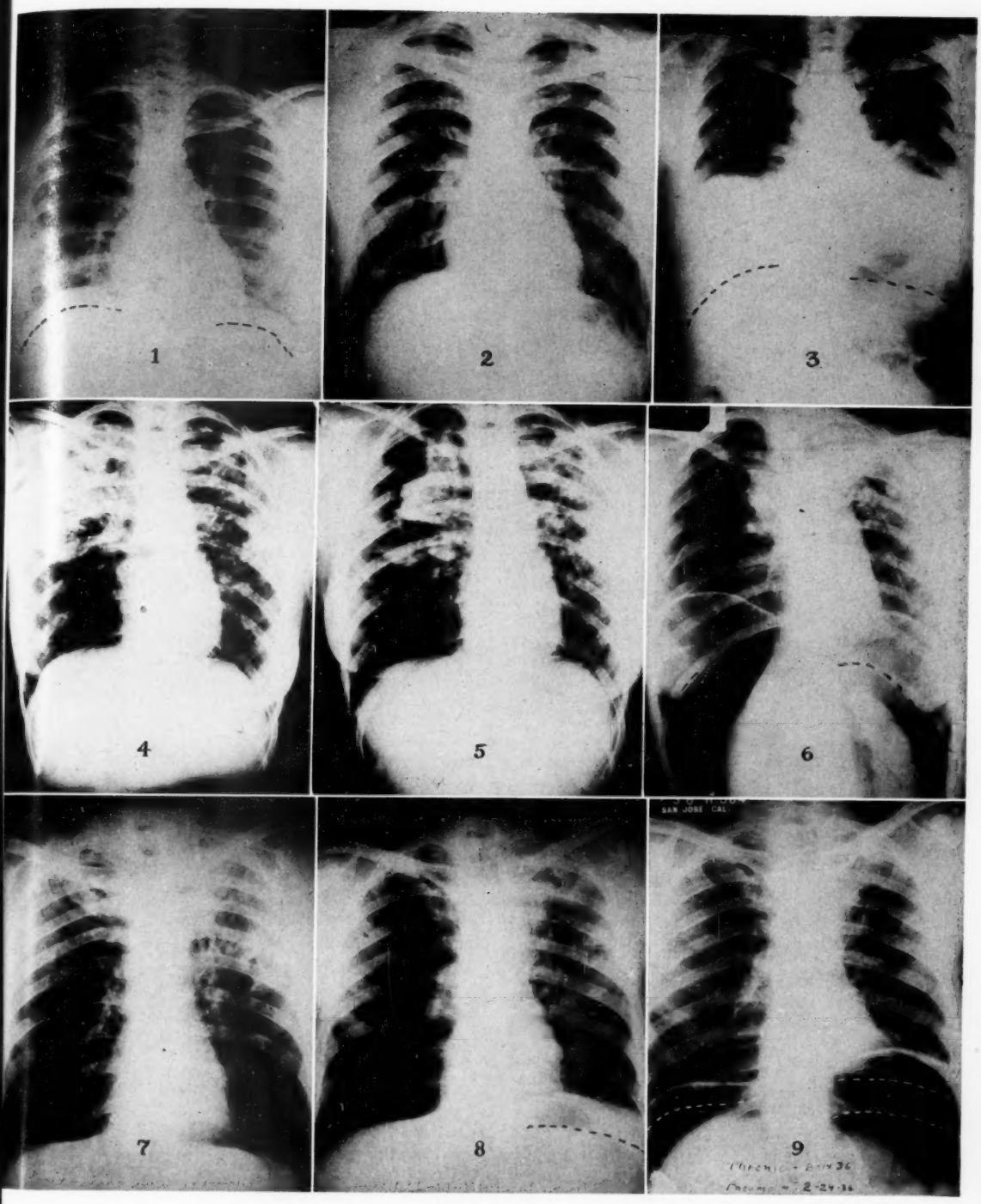

PLATE 1

our series these have been few. There seems to be little danger of puncturing a gut unless a loop of bowel should be adherent to the anterior abdominal wall at the site of the puncture. To our knowledge, this complication has not occurred in our series. Fluid is encountered in a small percentage of cases. There has been one case of adhesive peritonitis which eventually completely obliterated all free space. This caused the patient practically no discomfort at the time, and although it occurred over a year and a half ago, she has suffered no ill effects. Her pulmonary lesions are much improved. Moderate weight loss is rather frequently encountered. One patient died of an air embolus.

PLATE 2

Case 3. H. D., age 43. White male, musician.

Fig. 10. August 20, 1934. Extensive bilateral pulmonary lesions, more extensive on the right. Right artificial pneumothorax from January to October, 1935. Collapse entirely inadequate.

Fig. 11. September 18, 1935. Right phrenic nerve avulsed March, 1935. Good rise of right hemidiaphragm. Splinting of the right lung still considered inadequate and pneumoperitoneum was started in October, 1935. Pneumothorax abandoned. Sputum still positive.

Fig. 12. February 11, 1936. Note additional rise following pneumoperitoneum (4 months). Amount of sputum reduced and is now negative for acid-fast organisms. Film illustrates additional rise that can be obtained from pneumoperitoneum. Note the presence of peritoneal fluid.

Case 4. R. R., age 24. White student nurse.

Fig. 13. August 15, 1934. The patient was at bed-rest from December, 1933, to April, 1934. Pneumothorax was attempted without success in April, 1934. Right phrenic nerve was crushed in January, 1935. Poor rise. Cavity still open in June, 1935.

Fig. 14. February 16, 1936. Pneumoperitoneum started in June, 1935, and continued to date. Pneumoperitoneum has resulted in marked splinting and elevation of both leaves of the diaphragm. Dotted lines mark the original level. The cavity in the right subclavicular region is closed. Sputum is negative.

Case 5. Robert R., age 31. White male, newsboy.

Fig. 15. September 26, 1931. The patient was first seen at this time with an extensive involvement of the right lung. Pneumothorax not possible because of adhesions.

Fig. 16. June 9, 1933. Right phrenic nerve avulsion in January, 1933. Good rise as shown. However, it was not effective in controlling the lesion alone.

Fig. 17. August 28, 1934. Upper stage thoracoplasty July, 1933. This with phrenic nerve avulsion was temporarily adequate in controlling the lesion. Sputum negative. He was discharged in February, 1934, and followed at the clinic. Note the lower level of the diaphragm.

Fig. 18. September 12, 1935. Developed new lesion with large cavity at the right base. Sputum positive. Patient was readmitted and a pneumoperitoneum was started in October, 1935.

Fig. 19. February, 1936. Note the rise of the right hemidiaphragm with pneumoperitoneum (4 months). Sputum is negative. Cavity is closed.

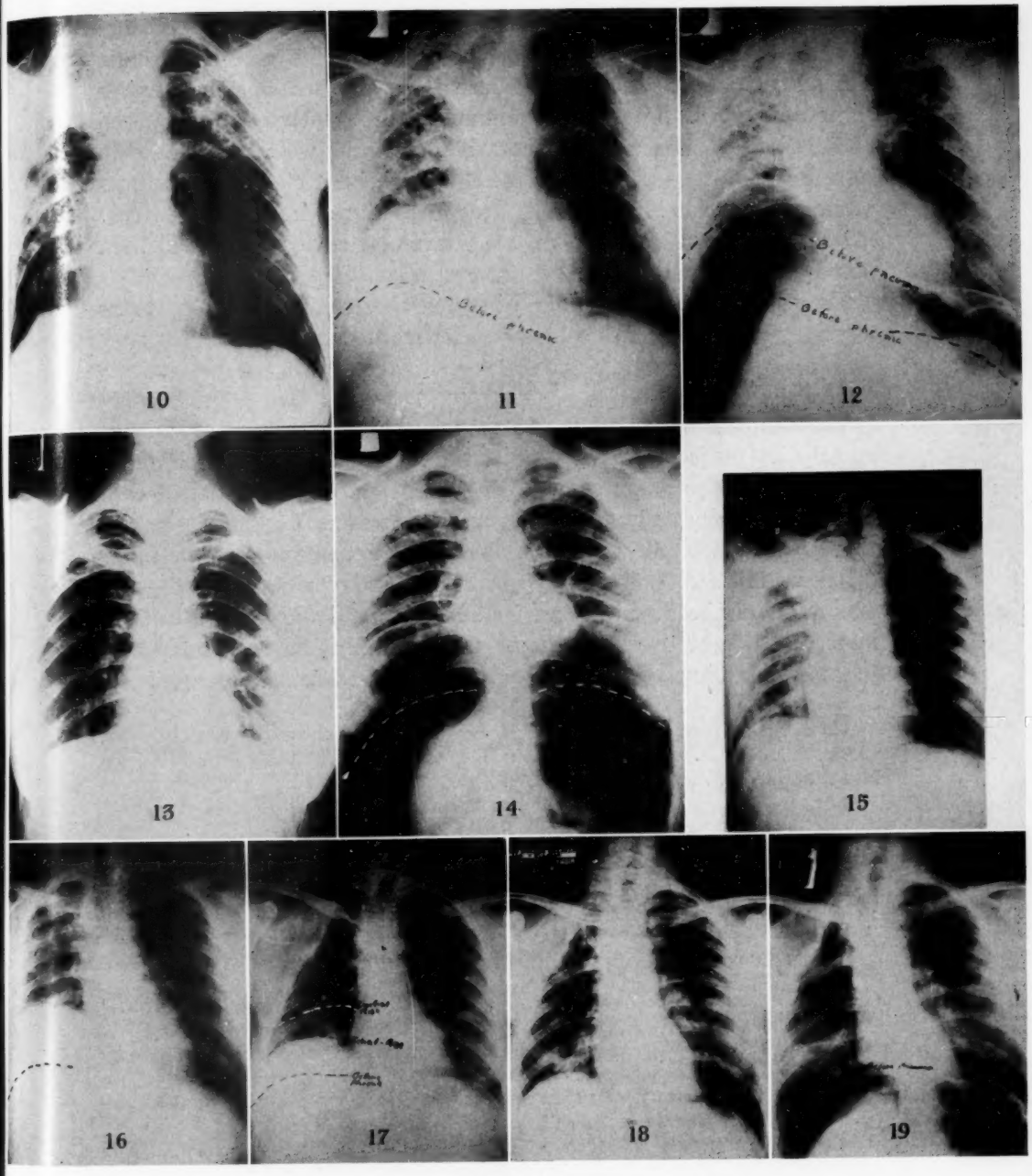

PLATE 2

This should be called a preliminary report because the procedure has not been used sufficiently long to determine its true therapeutic value. To date, however, three far-advanced cases have been made sputum-negative. Cough and sputum have frequently been diminished and the patient made more comfortable. Cavities which have failed to close by any other available procedure, have been closed by pneumoperitoneum. This is particularly true of basilar cavities. In one case it was effective in closing a large subclavicular cavity which had been present for two years.

The psychology on the group of patients for whom previously there was very little to offer, has also been of marked benefit.

CONCLUSIONS

The beneficial effect of the latter months of pregnancy upon pulmonary lesions is apparently due to the mechanical effect of elevating and splinting the diaphragm. The same effect can be obtained to a much greater degree by the use of pneumoperitoneum.

It has a particularly valuable application in patients who have a fairly extensive bilateral pulmonary tuberculosis and who cannot be given pneumothorax because of extensive adhesions and who cannot tolerate more drastic procedures of collapse therapy. It is also a valuable adjunct in obtaining a greater rise of the paralyzed hemidiaphragm.

The authors wish to express their appreciation for the kind assistance rendered by Drs. C. Bush, C. Mason, I. Gourley, R. Libby, and Hart of the Alameda County Institutions, and Miss M. Schuler of Alum Rock Sanatorium.

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THE EFFECT OF SPLENECTOMY ON TUBERCULOUS INFECTION IN MICE[1]

JESSIE MARMORSTON

The reports of the effects of splenectomy on resistance to infection are contradictory. The mass of evidence points, however, to a definite depression in both the natural and acquired resistance of animals to spontaneous or induced infection with certain microörganisms following splenectomy.[2]

Bardach (2) observed that splenectomized dogs succumbed in a very high percentage (80 per cent) of instances to an induced anthrax infection. Only 20 per cent of the controls died. Morris and Bullock (3) studied the effects of splenectomy in immature and mature rats on the mortality to spontaneous infection with *Bacterium enteritidis* (Gaertner) during the course of an epizootic in their laboratory stock. Their experiments suggest that removal of the spleen lowers the resistance of the rat to the spontaneous infection. In view of the significance of the experiments, it is regrettable that no mention is made in the author's report as to the presence or absence of anaemia following splenectomy in the rats used. During the past few years it has been demonstrated that *Bartonella muris* anaemia follows removal of the spleen in almost all strains of rats used for laboratory purposes (4) (5) (6) (7) (8).

The factor of latent infections was eliminated in the experiments of Marmorston (9) on the effect of splenectomy in mice to a subsequently induced *Bacterium enteritidis* (Gaertner) infection. Marmorston observed that in a strain of mice highly resistant to bacterial infection, the removal of the spleen depressed the natural resistance to a subsequently induced infection with *Bacterium enteritidis*. In a strain of mice highly susceptible to bacterial infection the removal of the spleen did not affect the natural resistance to a subsequently induced infection with *Bacterium enteritidis*. Kurlow (10), Courmont and Duffau (11), observed in rabbits no definite effect of splenectomy on induced infections with

[1] From the Department of Pathology, Cornell University Medical College, New York City.

[2] For a detailed review on this subject see monograph by Perla and Marmorston (1).

staphylococcus, pyocyaneus, streptococci and chicken-cholera. Their experiments, however, are difficult to evaluate because the number of animals was small.

Splenectomy in rats, dogs, cats and rabbits, depressed the resistance of these animals to a subsequent infection with *Trypanosoma brucei* (Bradford and Plimmer (12), Davis (13)). Regendanz and Kikuth (14) found that *Trypanosoma lewisi* infection in splenectomized rats was more severe than in normal rats. Perla and Marmorston (15) observed the effect of splenectomy on infection with *Trypanosoma lewisi* when the operation was performed at various intervals before infection, and determined the effect of autoplastic splenic transplants on the infection in splenectomized rats. The rats used were carriers of *Bartonella muris* and splenectomy in these rats resulted in *Bartonella muris* anaemia. Reproductive forms of the parasite were observed several days longer in the splenectomized than in the normal rats, and the duration of the infection in the former rats was twice as long as in the normal groups. Forty-eight days after splenectomy the infection with *Trypanosoma lewisi* is less severe than in the early period. Apparently some compensatory mechanism has been established, but this is less effective in combating infection than the normal splenic tissue. Splenic autotransplants introduced four weeks prior to splenectomy raise the resistance of rats to a subsequent *Trypanosoma lewisi* infection. Taliaferro, Cannon and Goodloe (16) observed the course of *Trypanosoma lewisi* infection in splenectomized rats, noninfected with *Bartonella muris*. Prolongation of the infection was observed in splenectomized rats of both carrier and noncarrier stock, but the period during which reproductive forms of parasites were observed in the blood was not increased in the splenectomized rats of noncarrier stock.

Foot (17) studied the effect of splenectomy on bovine tuberculosis in rabbits. The operation was performed two weeks before infection. The rabbits were injected intravenously with 0.2 mgm. of a culture of bovine tubercle bacilli two weeks old. The lungs of the splenectomized rabbits contained a great number of discrete, firm miliary tubercles, whereas in the control group, the lungs contained areas of caseous pneumonia. The course of the disease was not conspicuously altered, the actual differences in the length of life after inoculation in the splenectomized and normal animals being less than one week. The liver showed more extensive lesions in the operated than in the control animals.

Lewis and Margot (18) described experiments supporting their opinion

that removal of the spleen in mice greatly increased resistance to infection with bovine tuberculosis, induced two weeks after operation. The infection in splenectomized mice, they state, tended to remain localized as contrasted with an almost septic type of disease which occurred in the normal animals. The animals in each group that lived more than 30 days often had "exudative" lesions. This apparently increased resistance was diminished by the feeding of fresh spleen of mouse or sheep. (In our own experience, fresh spleen is irritating and causes profound gastroenteritis.) Recently Watson (19) has studied the effects of aqueous extracts of raw spleen on the course of experimental tuberculosis of the human type in guinea pigs, and comes to the conclusion that the duration of the disease is considerably prolonged by repeated injections of extract. Details concerning the method of extraction, the animal from which splenic tissue was obtained and the amounts administered are not mentioned.

The purpose of the experiments reported in this communication was to study the effect of splenectomy in mice on natural resistance to tubercle bacilli.

Effect of Splenectomy in Mice on the Course of an Induced Infection with Bovine Tubercle Bacilli

A series of 28 adult mice was divided into three groups. Twelve were splenectomized with aseptic technique, through a vertical incision in the left upper quadrant of the abdomen; in eight a laparotomy was performed and the spleen exposed and replaced; and eight were used as normal controls. One week after operation, all were infected intraperitoneally with 0.1 mgm. of bovine tubercle bacilli.

The changes induced in mice by a tuberculous infection, bovine or human, are primarily limited to the site of inoculation, the lungs, the liver and the lymph nodes. Tubercles such as are found in other mammals do not occur in the mouse and only a few epithelioid cells may appear in the liver. Massive necrosis of liver tissue may occur without previous tubercle formation. Proliferation of Kupfer cells and periportal accumulations of cells resembling lymphocytes are the usual changes found in the liver. The lesions in the lung are pneumonic in character, and both polymorphonuclear leucocytes and large fat-laden macrophages accumulate in the alveoli. The lesions are more severe after infection with the bovine than with the human type of tubercle

bacilli. The local peritoneal lesions were slight in both groups; some thickening of the omentum and a small caseous node in the mesentery were occasionally observed.

When an animal died in any group, one of each of the other groups was killed and the lesions compared. The experiment was terminated three months after the infection was induced and the surviving animals were killed and examined at that time. The mice used in this and the following experiment were carriers of *Eperythrozoan coccoides*, *Bartonella muris* and *Klossiella muris*.

There was a definite decrease in the resistance of the splenectomized mice (see table 1). Seven of the twelve splenectomized mice succumbed in 18 days, 46 days, 48 days, 63 days, 69 days, 74 days and 76 days

TABLE 1

The effect of splenectomy in mice on the course of a subsequently induced infection with Mycobacterium tuberculosis (Bovine Ravenal)

	NUMBER OF MICE	NUMBER OF MICE THAT DIED SPONTANEOUSLY OF TUBERCULOSIS	NUMBER OF MICE, INFECTION ABSENT	EXTENT OF DISEASE AT THE END OF EXPERIMENTAL PERIOD		
				Slight	Moderate	Severe
Splenectomy	12	7	0	4	2	6
Laparotomy	8	0	2	4	2	0
Normal controls	8	0	3	3	2	0

respectively, after the infection was induced. The mice in which a laparotomy was performed showed about the same extent of tuberculosis as the normal controls.

The distribution of the disease process was noteworthy. The lungs, lymph nodes and liver were more extensively involved in the splenectomized group than in the normal.

Effect of Splenectomy in Mice on the Course of an Induced Infection with Human Tubercle Bacilli

A series of 18 mice was divided into three groups. Eight were splenectomized, in six a laparotomy was performed and four were used as normal controls. All the mice were infected with 0.1 mgm. of a human type of tubercle bacillus intraperitoneally.

None of these animals died spontaneously but all were killed at the end of three months.

In these animals as in those that received bovine tubercle bacilli, the lungs, lymph nodes and liver were more extensively involved in the

splenectomized group. Microscopically the smaller lesions were primarily accumulations of lymphocytes with little or no giant cell formation and no caseation. Some alveoli contained large lipoid-laden macrophages.

The kidneys in three of the splenectomized mice were large, yellowish-brown in color and had gray patches in the cortex. In microscopical sections intense infection with a coccidium (*Klossiella muris*) was found. All the splenectomized mice showed similar microscopical changes in the kidneys. In the control group only an occasional animal was infected with *Klossiella muris* as determined by the microscopical appearance of the kidneys.

TABLE 2

The effect of splenectomy on the course of a subsequently induced infection with Mycobacterium tuberculosis (Human H-37)

	NUMBER OF MICE	NUMBER OF MICE, INFECTION ABSENT	EXTENT OF THE DISEASE AT THE END OF THE EXPERIMENTAL PERIOD*		
			Slight	Moderate	Severe
Splenectomy	8	1	0	3	4
Laparotomy	6	1	3	0	1
Normal controls	4	1	2	1	0

* The mice were all killed at the end of three months.

The Effect of Splenectomy in Mice Free from Eperythrozoan coccoides, Bartonella muris and Klossiella muris on the Course of a Subsequently Induced Infection with Bovine Tubercle Bacilli

In the course of the first two groups of experiments it became apparent that the mice used for these studies were carriers of latent infections influenced adversely by splenectomy. Latent infections with three microörganisms were found: *Eperythrozoan coccoides*, a parasitic infection of the red cells that did not produce an anaemia and that manifested itself only after the removal of the spleen (20) (21) (22); *Bartonella muris*, producing a mild infection in the mouse without anaemia and becoming manifest toward the close of infection with *Eperythrozoan coccoides*, (22); and *Klossiella muris*, a coccidium parasite producing lesions of the kidney, perhaps intensified by splenectomy (23).

The effect of splenectomy on the course of bovine tuberculosis was studied in a stock of mice found to be free from these infections.[3]

[3] These mice were kindly given us by Dr. Leslie T. Webster of the Rockefeller Institute for Medical Research.

Eighty four mice of this stock were divided into three groups: 30 were splenectomized, in 25 a laparotomy was performed and 29 were used as controls. All were injected intraperitoneally one week after operation with 0.1 mgm. of a culture of *Mycobacterium tuberculosis* (Bovine Ravenal).

Blood smears were examined every second day for the presence of *Eperythrozoan coccoides* and *Bartonella muris* and were found negative.

The kidneys of all mice were carefully examined for the presence of *Klossiella muris* and in no instance was this infestation found.

Of 54 normal and operated control mice only 6 mice died spontaneously of tuberculosis at 90, 95, 98, 125 and 154 days respectively. At the end of 164 days after injection, all those that had survived were killed and

TABLE 3

The effect of splenectomy in mice free from latent infections on the course of a subsequently induced infection with Mycobacterium tuberculosis (Bovine Ravenal)

	NUMBER OF MICE	NUMBER OF MICE THAT DIED SPONTANEOUSLY OF TUBERCULOSIS	EXTENT OF DISEASE IN MICE KILLED AT END OF EXPERIMENTAL PERIOD (KILLED AT END OF 164 DAYS)		
			Slight	Moderate	Severe
Splenectomy	30	11	0	6	13
Laparotomy	25	4	10	4	7
Normal controls	29	2	15	7	6

autopsied. Of the 48 killed at this time, in 35 the infection was slight, in 11 it was moderate and in 13 it was severe and extensive.

Of the 30 splenectomized mice, 11 died spontaneously at 40, 45, 48, 52, 63, 65, 68, 73, 87, 106 and 135 days respectively and the surviving 19 were killed at the end of the experimental period. Of the 19 surviving mice which were killed, in no instance was the disease mild, as determined by the extent of the lesions; in 6 the disease was moderate but in 13 it was extensive.

The tuberculous lesions in the liver and lungs were more severe in the splenectomized animals than in the nonsplenectomized mice.

These results confirm the earlier experiments performed in mice that were carriers of latent infections. In mice free of *Eperythrozoan coccoides*, *Bartonella muris* and *Klossiella muris*, splenectomy lowers the natural resistance to a subsequently induced infection with *Mycobacterium tuberculosis* (Bovine strain).

SUMMARY AND CONCLUSIONS

Removal of the spleen in mice diminishes natural resistance to a subsequently induced infection with human or bovine tubercle bacilli.

The results of experiments were essentially the same in mice that were carriers of latent infections with *Eperythrozoan coccoides* and with *Bartonella muris* and those that were free from these infections.

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THE CERTIFIED DIAGNOSIS OF TUBERCULOSIS

Further Practical Studies on the Detection of Tubercle Bacilli

MORRIS GREENBERG[1] AND MAURICE L. COHN[1]

In 1928, Corper (1) emphasized the significance of methods for demonstrating tubercle bacilli for the certified diagnosis of tuberculosis. He showed the relative lack of delicacy of the microscopical examination of the stained smear, which has the advantage of speed over guinea-pig inoculation and culture methods. The latter two methods are capable, with equal efficiency, of disclosing small numbers of tubercle bacilli in specimens; the culture, however, possessing the advantage of economy and of revealing tubercle bacilli as such (2).

In spite of the numerous valuable contributions on the subject of cultural diagnosis within the past decade, textbooks and various reports still deal with this subject in vague terms and include materials and media proved obsolete at least ten to twenty years ago. Some of these are entirely misleading in the light of fundamental facts. For illustration, a recent note (3) advises that "as sputum frequently contains many other micro-organisms, one can destroy them for the most part by treating it with 4 per cent antiformin. After an hour the material is centrifugated, and the sediment planted on laboratory mediums. Antiformin may be dispensed with if Petroff's medium, which contains gentian-violet, is used. This inhibits the growth of micro-organisms other than tubercle bacilli, and, therefore, permits one to plant sputum directly on it." Suffice it to say, antiformin is entirely unsuited for recovering small numbers of tubercle bacilli; Petroff's medium cannot be used without first destroying contaminators by means of sodium hydroxide or other suitable reagents, and finally the amount of gentian-violet in this egg medium retards the growth of small plantings of tubercle bacilli (4) (5). This medium served a very good purpose when introduced in 1915, but progress has proved it inadequate.

Now and again, practice requires that we evaluate various techniques and methods, primarily to disclose the latitude permitted and also what recommendations may be made as to the essentials and nonessentials in

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the routine of the sanatorium and the clinic. It is obvious that striking differences are disclosed between the microscopical examination of the stained smear and the guinea pig or culture. Can we expect striking differences in results between the various methods of staining smears, and where in this category can concentration methods be placed for the purpose of practice? It was the object of this study to elucidate this question by comparative experimental observations.

Among those cumbersome techniques which must again be evaluated frequently for practice are the so-called concentration methods, usually time-consuming and fraught with numerous possibilities for confusion. Within recent years only isolated techniques on such methods have been described and reported. Among these are included a dilution-flotation test (6) which is highly recommended for practice. This method which makes use of dilution and flotation by means of xylol, benzene, gasoline, and ligroin, and a mechanical shaking device to disperse the hydrocarbon through a diluted, sodium-hydroxide digested specimen, claims an efficiency 200 times better than the microscopical examination of the stained smear and alleges to reveal the presence of as few as 1,000 bacilli in a 24 hour specimen. It is stated "such results approach quite closely the recognized sensitiveness of guinea pig inoculation as well as the not too well determined sensitiveness of the culture method."

In order to evaluate the various smear methods, concentration and culture methods, the following comparative tests were made on the same natural specimens:

1: Various staining methods were compared, including the Ziehl-Neelsen and Spengler methods.
2: Comparison of the stained smear with the dilution-flotation method.
3: Comparison of the smear with the dilution-flotation and culture. In addition, comparison and tests were also conducted with specimens prepared for the purpose by adding graded amounts of fine suspensions (7) of tubercle bacilli to negative sputa.

It is not the purpose of this report to give elaborate details of all the experiments performed but rather to present the pertinent results in a few tabulations that will prove of practical value to others either in pursuing further studies or in applying these findings to practice.

In one of our experiments to determine the value of counterstains in increasing the efficiency of the findings, 123 specimens of sputum were examined by the direct smear method. The slides were prepared in the

usual manner and one-half of each slide was counterstained with methylene-blue and the other half with picric acid. Each half was examined for at least fifteen minutes unless ten or more bacilli were found in a shorter period of time. The results were, briefly: methylene-blue side, 39 positives; picric acid side, 48 positives. These findings verify those of earlier observers who maintain that picric acid counterstaining yields a higher percentage of positive findings. In addition, it was noted that in the majority of cases more bacilli were found per field in the picric acid stained preparations. However, methylene-blue has the advantage of its differential staining quality, enabling the observer to distinguish cell structures, bacterial forms, etc., while picric acid merely acts as a diffuse stain. Where specimens are to be examined for tubercle bacilli alone, picric acid possesses advantages over methylene-blue as a counterstain.

In another experiment, the microscopical examination of the stained smear (carbol-fuchsin) with picric acid counterstain was compared with the dilution-flotation method on natural specimens from sanatorium patients. The dilution-flotation method used was as follows: a 24- to 72-hour specimen of sputum was collected in a sterile receptacle; a particle of this material was selected for examination by the direct smear and a 20 cc. sample was used for flotation test by placing it in an 80 cc. clean sterile test tube fitted with a clean sterile rubber stopper. To this was added an equal volume of 0.5 per cent sodium-hydroxide solution and the mixture shaken and digested in a water bath at 56°C. for 30 minutes, following which it was diluted to 60 cc. with sterile distilled water and 1 cc. of xylol was added. The mixture was shaken in an electrical shaking machine for 20 to 30 minutes and the tubes were permitted to stand until the opaque layer of xylol rose to the top. Invariably good separation occurred but occasionally when a xylol layer did not form the supernatant fluid was withdrawn, the specimen rediluted and shaken again. Smears from the entire xylol layer were made, using albumin fixative on the slide. After drying and fixing, ether was used to remove the excess xylol before staining. In a separate control experiment performed for the purpose of testing whether xylol or chloroform would change the acid-fast staining properties of tubercle bacilli, it was found that even prolonged contact with these reagents had no appreciable effect on the acid-fast properties.

In this series in which 314 natural specimens, including sputa, pleural fluids, etc., were examined by the direct smear and the above dilution-flotation method, the following results were obtained: by the direct

smear, 55 were positive; by the dilution-flotation method, 59 were positive. Those positive by both methods were 42; by the direct smear alone, 13; and by the dilution-flotation method alone, 17; giving a total of 72 positives by both methods. When considering the large number of specimens examined (314), and the fact that only four more gave positive results by the dilution-flotation method as compared with the simple direct smear examination, it would hardly suggest a practical advantage to use such a method.

The divergent results between the two methods are readily understood when it is recognized that natural tuberculous specimens are in their very

TABLE 1

Microscopical demonstration of tubercle bacilli in sputa to which graded suspensions of tubercle bacilli have been added: Comparative results of five methods

NUMBER OF TUBERCLE BACILLI PER CC. OF SPECIMEN*‡ (8)	DIRECT SMEAR METHOD		DILUTION-FLOTATION TEST*	CHLOROFORM SEDIMENT (9) TEST*	NaOH DIGESTION CENTRIFUGATION AND EXAMINATION OF SEDIMENT*
	Methylene blue counterstain	Picric acid counterstain			
100,000,000	5†	50	1000	1000	1000
10,000,000	1	8	300	100	100
1,000,000	0.02	0.07	5	1	2
100,000	0.03	0.06	0.15	0.06	0.1
10,000					
1,000					
100					
0					

* 10 cc. of sputum were used in each of the concentration tests.

† The numerals indicate the average number of bacilli found per field.

‡ 1 mgm. of bacillary mass contains about one billion tubercle bacilli in fine suspension.

nature irregular and nonhomogeneous so far as their content of tubercle bacilli is concerned.

In another experiment, 113 specimens, negative by the microscopical smear and dilution-flotation test, proved positive in 25 cases by culture alone. The culture method used was the sulphuric-acid-treatment potato medium (1) (two tubes planted from each specimen) and inspissated egg-yolk medium (8) (three tubes planted from each specimen). This experiment carefully performed from a comparative standpoint, all tests being carried out on the same specimen, again proved the efficacy of the culture over these other methods. It is interesting to note that in practically all the reports in the literature concerned with the demonstration of tubercle bacilli in the gastric washings or faeces

of children suspected of tuberculosis, either the culture method or the guinea-pig test was depended upon for diagnosis.

In order to obtain further information regarding particularly the quantitative relations between the results of the rapid microscopical smear examinations and various so-called concentration methods, these methods were compared experimentally on specimens which were artificially prepared to contain known amounts of fine suspensions of tubercle bacilli. The bacillary suspensions were well mixed with the sputum by prolonged shaking in an electrical shaking machine to insure as uniform and equal distribution as possible. Uniform portions were submitted to the different tests with the results recorded in table 1.

An examination of the results recorded in table 1 indicates that when large numbers of bacilli are present in a sputum, there are wide variations in the individual findings obtained. However, it is evident that, when graded amounts of bacilli are added to a sputum and this sputum is examined by the commonly used laboratory procedures as well as concentration or dilution-flotation tests, the point of extinction does not vary by a difference of a dilution of ten but occurs rather uniformly at a point approximating the presence of about 100,000 bacilli per cubic centimetre of specimen. This agrees well with the findings recorded previously by Corper (1) in earlier studies on the certified diagnosis of tuberculosis.

DISCUSSION

It is almost a dictum in medicine that the value of practical test or method of diagnosis or prognosis is dependent upon at least one or both of the following characteristics: it should be simply and speedily performed or it should make available information on a disease or group of diseases not obtainable by any other procedure. When considering the certified diagnosis of tuberculosis, it appears that there are three procedures to be evaluated in the light of our present-day knowledge. One of these, the microscopical examination of the stained smear, has held a favored place in private and sanatorium practice for speed and simplicity from the date of discovery of the tubercle bacillus over fifty years ago, although its limitations were not always recognized. Another, the use of the guinea pig as a diagnostic test animal, has enjoyed almost as long but not as universal popularity because of its selective specific accuracy for the examination of certain types of material (genitourinary specimens) and it supplied in delicacy and specificity what it lacked in

speed and simplicity. Finally, after numerous futile efforts, culture methods were developed which under carefully performed quantitative tests proved to be equal in delicacy to the guinea pig as a test and possessed certain definite advantages both economically and practically. During the period of development of culture methods to a point of high efficiency, there have been numerous attempts to employ some means of increasing the number of bacilli in a specimen to be examined microscopically in the stained smear by concentrating the bacilli in such a specimen by either attempting to concentrate them in a sediment or by collecting them in an intermediate zone of a watery and oily layer, or by floating them on a brine or by a combination of dilution and flotation. Such procedures usually involve time and multiple manipulations with the added possibility of introducing the universally present acid-fast saprophyte to confuse the value of the test. That the guinea pig and culture when properly used surpass both the microscopical smear examination and so-called concentration methods is evident from most of the recently performed empiric tests with natural specimens. Thus, a recent report (10) uses 100 sputa "in which *B. tuberculosis* had previously been demonstrated in the sputum but which had been negative by direct smear on three consecutive occasions" and finds the gasoline concentration test (GCT) and culture positive in 31, the GCT positive and culture negative in 6, and culture positive and GCT negative in 18. In 100 cases in which *B. tuberculosis* had never previously been demonstrated in the sputum, both were positive in 6, GCT positive and culture negative in 3, and GCT negative and culture positive in 8. This is illustrative of numerous examples in which the actual quantitative value of the methods used was unknown and in which tests were performed only on empiric specimens which, because of their very nature, were bound to give inconsistent and irregular results; yet the superiority of the culture is evident in both series of specimens tested, while the original proponent of the concentration method used indicated its equivalence to culture methods. When, however, tests are performed, as was done in the experiments recorded in our study, with specimens to which graded amounts of bacillary suspensions are added, it is evident that concentration or dilution-flotation methods do not achieve a concentration of ten to one over the microscopical smear examination alone (see table 1) (11) while culture and guinea-pig tests are approximately over a thousandfold more delicate than these tests, although they are admittedly slow in disclosing the desired findings.

SUMMARY

1. In the majority of cases, picric acid as a counterstain proved superior to methylene-blue in the examination of sputa for acid-fast bacilli, although methylene-blue possessed the advantage of distinguishing cell structures and other bacterial forms.

2. The microscopical examination of the stained smears of 314 tuberculosis specimens proved equally efficient to a dilution-flotation method.

3. The culture, properly performed, is superior to microscopical methods. In an experiment performed on 113 negative specimens by direct smear and dilution-flotation test, 25 proved positive by culture.

4. Control experimental tests with negative sputa to which were added small graded amounts of fine suspensions of tubercle bacilli revealed that there is not a 10 to 1 concentration of bacilli attained by various concentration methods as compared to direct smear examination.

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BOOKS

WILLIAM SNOW MILLER: *The lung. Pp. xiv + 212, with 152 illustrations, 20 of them colored, Charles C. Thomas, Springfield, Illinois, 1937, cloth, $7.50.*

By B. F. KINGSBURY

It is entirely fitting that a scientist should bring together in a single volume the significant results of a life-time of work. This has been done in the present volume upon "The Lung" by Professor emeritus William Snow Miller of the University of Wisconsin, who through a period of nearly fifty years has devoted much of his research time to an elucidation of the anatomy of the lung. This little volume is not, however, a mere compilation of Doctor Miller's numerous contributions to an understanding of the structure of the lung. It is a logical and orderly progression through twelve chapters, from a concise statement of the gross anatomy to a consideration in the final chapter (xii) of the structural and functional unit which Miller regards as the primary lobule.

The work is illustrated by 152 figures, 20 of them in colors, carefully selected. Many of them are original or reprinted from figures previously published by the author. The paper and printing are excellent, typographical errors few. The context is supplemented by a bibliography of 222 titles, and the whole is fully indexed, author and subject.

The twelve chapters deal with (1) the lungs, (2) the trachea and bronchi, (3) intrapulmonary bronchi and bronchioles, (4) the air spaces, (5) the blood vessels, (6) the lymphatics, (7) the pulmonary lymphoid tissue, (8) the nerves, (9) the pleura, (10) key points, (11) historical sketch, and finally (12) the acinus. In this succession of chapters, the presentation is so logically developed that it is difficult for the reviewer to select any one feature for emphasis.

Aside from the structural plan of the lung so well portrayed by the figures 54 and 114, may be mentioned: the tracheal and bronchial musculature, the elastic tissue of the lung and pleura, the structure of the pleura and the lymphatic drainage. The old and vexed question as to the lining of the respiratory chambers (alveolar ducts, atria, alveolar sacs, alveoli), recently revived, is decided by Doctor Miller in favor of a continuous epithelium. Non-nucleated plates, however, are not present. The source of "alveolar phagocytes" is not fully discussed but an epithelial origin is discounted. "Foam cells" within the alveolar spaces are regarded as desquamated cells from the respiratory epithelium. Pores in the alveolar wall are artifacts or results of

such cell desquamation. Significant is the discussion of the relation of the bronchial and pulmonary circulations.

As a concise and accurate presentation by a master of the subject, the book will be a valuable addition to the library of the clinician and pathologist, as well as the anatomist and histologist. From an even superficial examination of this work, it is obvious that for Doctor Miller the structure of the lung is far from being a closed chapter. Further contributions by him may be confidently expected.

HENRI JOLY: *La collapsothérapie hypotensive appliquée au traitement médico-chirurgical de la tuberculose pulmonaire. With 10 schemas and 36 figures in the text, pp. 314, Gaston Doin & Cie, Paris, 1936, paper, 50 fr.*

By J. BURNS AMBERSON, JR.

Practitioners of collapse therapy by pneumothorax or more radical methods should possess technical skill and thorough knowledge of pulmonary mechanics and of the pathology of tuberculosis. Skill comes more easily than the knowledge, and both more easily than the wisdom with which they should be applied. Those who subscribe to this view will find in Joly's book much substance for thought; those who do not might well read it for the beginning of their enlightenment. The treatment of the subject is thoroughly scientific and is not colored by enthusiasm. The fundamental premise is that hypotensive pneumothorax, affording relaxation of the lung, is physiologically rational and clinically effective in properly selected cases, whereas compressive pneumothorax is not just the reverse but even worse, since it favors progression of the disease in the opposite lung, pleural effusions and rupture of the pleura. Such condemnation of compressive pneumothorax is too severe, because gentle compression (+2 to +6 or +8 cm. water) maintained by frequent refills avoids undue hazards and often suffices to accomplish the desired result. Nevertheless, in a logical and comprehensive discussion, the author makes out a strong case for the efficacy of low tensions and convinces one that precipitate use of positive pressure is unwarranted. This is based largely on the reasoning that cavities become closed by concentric contraction of their walls. The conception that cavities become bridged over and obliterated by having their walls approximated is dismissed with the statement that this has never been proved. The play of forces which permits collapse of the lung, the ease or difficulty with which various types of lesions may be affected, and the mechanisms of healing are discussed in excellent and orderly manner.

Aside from pneumothorax, the action of which is a pattern to be imitated by other measures, specific consideration is given phrenic nerve paralysis, scaleniotomy, alcohol injection of the intercostal nerves and apicolysis with paraffin plombage. Each, alone or in combination, is recognized to have a

limited place. Phrenic nerve paralysis has been disappointing in Joly's experience and its results are uncertain; it has the disadvantages of disabling healthy parts of the lung and adding to the risks of a later thoracoplasty, should this be necessary. The most interesting conception presented is that of "hypotensive" thoracoplasty. By this is meant limited rib resection to relax selected underlying cavity-bearing lung which then may heal in the natural way. Ample time must be allowed before the ribs are permitted to regenerate, and this is accomplished by treating the periosteal beds with ten per cent aqueous formol solution at the time of operation; or in some cases extraperiosteal resection is performed. Some good results are demonstrated and one is impressed that the method represents a real advance in certain situations. The great advantage and necessity of sanatorium treatment in all cases requiring collapse therapy are stressed. Joly effectively destroys the idea that collapse therapy is a standard method for mass treatment of tuberculosis and establishes advanced conceptions on the basis of which thoughtful and logical discrimination can be applied in each case.

BENJAMIN GOLDBERG: *Clinical tuberculosis. Edited by Benjamin Goldberg with the collaboration of 33 contributors. Volumes 2, paged in sections comprising altogether pp. 1550, with 640 half-tone and line engravings and 9 full-page colored plates, Philadelphia, F. A. Davis Company, 1935, fabrikoid, $22.00.*

By EMIL BOGEN

The two volume encyclopedia of clinical tuberculosis produced by Doctor Goldberg and his thirty-three collaborators constitutes one of the most stimulating presentations of modern tuberculosis lore that has appeared for a long time. Almost each contributor manages to put in the course of his chapter some new conception or revolutionary assertion to startle the reader from too ready acceptance. This radical espousal of unproven innovations is both refreshing and appealing, but it is, perhaps, fortunate that its high price will tend to prevent it from falling into the hands of general practitioners and novices in tuberculosis who might too readily accept its provocative assertions for gospel truth.

The binding and arrangement are excellent, the typography and illustrations clear and attractive, and the index comprehensive, but typographical errors are present, the roentgenograms appear indiscriminately as positives and as negatives, and there is no table or index to the numerous reproductions. Excellent bibliographies are appended to some chapters, but others are scant or completely absent. Most of the contributors hail from Chicago, a few from New York and Pennsylvania, and one from Colorado. Space forbids adequate discussion of each of the moot questions brought up in the forty-eight chapters

of this work, or even a full appraisal of the exceptionally fine presentations encountered in certain chapters, but a few of them might be mentioned.

A wealth of authoritative data and judicious interpretation of the available statistics bearing on the epidemiology of tuberculosis opens the book. The stress on inherited resistance in the children of tuberculous subjects appears a rather questionable explanation, however, for the mechanism of a well demonstrated phenomenon.

The elaborate life cycle described for the tubercle bacillus, with streptococci, diphtheroids and even enteric organisms appearing as disguises assumed by the elusive changeling, remains a strictly personal exposition of views still generally rejected. The chemistry and cultural characteristics of the classical acid-fast rod are given scant attention, and the changes in the differential blood count in infected animals and humans which Schilling, Sabin, Medlar and others have so strongly stressed is not even mentioned.

Considerable differences of opinion are expressed in different chapters regarding the validity of the Ranke schema for the pathogenesis of tuberculosis, the primary localization, secondary generalization and tertiary isolation admired by the pathologist being replaced with a primary dissemination, and secondary localization with only intermittent and accidental later spreads in the clinical description of haematogenous tuberculosis.

The appealing and plausible conceptions of Coryllos of the pathogenesis of cavitation in tuberculosis are presented by the author with a wealth of citation of physiological facts, pathological inferences, and surgical recommendations. It is sad that the pathologist and the other surgeons writing in this group maintain an ominous silence on this subject. The qualitative classification of tuberculosis presented by Ornstein and Ulmar with a profusion of illustrative clinical case reports receives more consideration, both critical and enthusiastic, from their colleagues.

The rôle of allergy in tuberculosis receives a highly varied treatment in different chapters; scouted by the pathologist, stressed by the clinicians, endorsed by the immunologist and feared by the pediatrician, its highly debatable position is apparent. The differences of opinion expressed on the therapeutic value of tuberculins or the prophylactic value of BCG by different contributors are accordingly quite understandable.

The cited increase in the alkali reserve in tuberculosis, contrary to the finding of most workers, and the recommendation of a holder for cigars and cigarettes, with the consequent smoking further into the stump which this allows, may be questioned. Special diets seem to have proven their worth in intestinal and in skin tuberculosis, but controlled studies to support the elaborate regimen proposed are still needed. Congenital cystic disease of the lungs is ignored both in the differential diagnosis of tuberculosis and in the aetiology of idiopathic pneumothorax.

Among the chapters on *Extrapulmonary Tuberculosis*, the treatment of laryngeal tuberculosis is particularly complete, especially in its bibliography. Among the newer procedures recommended in tuberculous patients where surgery may be contemplated are bronchoscopy, electrocardiography and intravenous urography. The treatment of diabetes in the tuberculous is fully discussed, but an interrelationship between the diseases is viewed critically.

The extensive experience of the Matsons with artificial pneumothorax and the more conservative measures in collapse therapy is admirably presented, with abundant citation of cases and of statistical data. Followers of Alexander may wish that the temporary phrenic operation were given more consideration, and that intercostal neurectomy might at least be mentioned. The confidence and optimism with which partial and complete thoracoplasties are recommended makes one wonder at the complete omission of any reference to the Adams-Vorwald operation of bronchial occlusion, or to lobectomy or pneumectomy which have been suggested in certain cases.

The two chapters on *Physical Diagnosis* are divided, for no obvious reason, and contain repetitions suggesting the refurbishing of older articles for this volume without adequate scissors and blue-pencilling. The subjective sensory reflex symptoms of Pottenger are quoted at considerable length, but no mention is made of the objective signs of muscle spasm and atrophy described by the same author.

The chapter on *Prophylaxis* emphasizes the contagiousness of tuberculosis, in strange contrast to the following chapter on *Home Treatment* by the same author, in which the very possibility of adequate institutionalization of all open cases is scouted. Home treatment, strange to say, is advised especially for the wealthy, who are apt to be best able and willing to profit from sanatorium care.

The discussion of *Medicinal, Symptomatic and Tuberculin Therapy* emphasizes the value of calcium and vitamin D, which still require verification, and omits mention of vitamin C, which is probably of more importance, at least in intestinal cases. The treatment of pulmonary haemorrhage with morphine, emetine and coagulants may be questioned. Tuberculin therapy is described only to be condemned in this chapter, and the chapter entitled *Tuberculin* is concerned only with its diagnostic application.

Although conservative and somewhat apologetic, the chapter on *Climate* insists on its value and suggests possible extensions of its use. No consideration is given to the possibilities of air-conditioning in securing desired climatic conditions.

Controversial matters abound in this publication, but it is just in this that its chief merit may be found to lie. No other book in recent years has been so replete with stimuli for further investigations and of suggestions as to the direction in which future work is indicated. Without accepting Doctor Gold-

berg's pessimistic avowal that tuberculosis will continue to rank as one of the outstanding scourges until a specific remedy for the disease is discovered, we may recognize the importance of research in accelerating the decline that has occurred. If but a few of the problems for which he and his collaborators have so boldly presented tentative answers may be solved within the near future as a result of work stimulated by this daring sally, we may well be grateful for the labors which it represents.

A. CALMETTE: *L'infection Bacillaire et la Tuberculose chez l'homme et chez les Animaux. Étude Biologique et Expérimentale Vaccination Préventive; 4th edition entirely revised and completed by A. Boquet and L. Nègre. With 33 plates and 51 illustrations in the text, pp. viii + 1024, Paris, Masson et Cie, 1936, cloth, 175 francs.*

By MAX PINNER

Professor Calmette's textbook needs no introduction to the readers of the *Review*. Undoubtedly most of them are familiar with previous editions or with the English translation. Anyone who is actively interested in the fundamentals of phthisiology has consulted this standard work. It has always been an unfailing aid for basic information. The information it offers is in many regards considerably different from the current teaching in this country. But the important thing is that it is the book of *one* man, of a true scientist with a wealth of first-hand information, a book decidedly written with a pen and not with scissors as is so often the case with textbooks. It would be quite futile, therefore, to point out differences in French and American teachings, to enter into controversies. A valid refutation could not be undertaken on a smaller scale than that of the book; and this would be an appalling task.

One of the great values of Professor Calmette's text is the fact that it is a complete and logical exposition of the French teachings. It is for us *the* authoritative statement of all those topics on which disagreement exists between the two countries, such as portal of entry, filterable virus, BCG, to mention only the outstanding ones.

The fourth edition, prepared by Doctors A. Boquet and L. Nègre, is a worthy successor to the last edition of 1926. The editors have digested a tremendous amount of work that appeared during the last decade, and they have added it to their master's text, truly *avec le sentiment de remplir un pieux devoir envers la mémoire de notre Maître.* The two editors, both famous in tuberculosis research, have completely modernized the book without detracting from its unity. This is probably the highest praise possible for such self-effacing work.

To return once more to the difference of opinions: any worker in tuberculosis may disagree with many of the tenets expressed by Calmette, Boquet, Nègre; but none can afford not to know them.

JOHN B. HAWES, 2ND, AND MOSES J. STONE: *The diagnosis and treatment of pulmonary tuberculosis. With a foreword by Richard C. Cabot. With 43 illustrations, pp. 211, Lea & Febiger, Philadelphia, 1936, cloth, $2.75.*

By CHARLES W. MILLS

In their preface the authors say that their purpose is to bring up to date a book of twenty years ago by one of them on the same subject—a book then characterized by Dr. R. C. Cabot as short but authoritative. They state their belief that there is need for such a book. They have fulfilled their purpose in all of these particulars, for the present book is condensed, authoritative, up-to-date and timely.

A brief summary will indicate the book's scope and arrangement. A short historical chapter is followed in order by chapters on *History Taking*, *Symptomatology*, *Physical Examination*, *Differential Diagnosis*, *Tuberculosis in Childhood*, *Roentgen-ray Diagnosis*, *Laboratory Methods*, *Sanatorium and Home Treatment*, *Treatment of Symptoms and Complications*, *Collapse and Compression Therapy*, *Heliotherapy*, *Climate*, *Specific Treatment by Serums*, *Vaccines and Drugs*, and *Diet*. These chapters very expertly cover what may be considered subjects fundamental to any general book, however brief, on tuberculosis. Then follow a few chapters on what might be called odds and ends;—*Rehabilitation*, dealing with occupational therapy and farm colonies; the *Heart in Pulmonary Tuberculosis; Tuberculosis in the Aged; Marriage and Pregnancy;* and *Dangerous Trades*. Of course such odds and ends of so large a subject could be indefinitely added to, but the above comprise the authors' selection of those which they consider important enough to include. They state in their preface that they have purposely omitted, as out of place in a simple textbook of this sort, such intricate subjects as immunity, resistance, allergy, etc. There is finally a chapter on the *Prevention of Tuberculosis*, dealing with public health aspects.

At the end of each chapter is a concise summary of the contents and a bibliography which is called "Suggestions for Supplementary Reading." Both of these features are well done and helpful. There are 43 illustrations, most of them from X-ray films, well reproduced.

The chapters on *History Taking* and *Physical Examination* contain many helpful and practical hints. In those on diagnosis, an excellent balance is kept as to the value of the various methods, and the need of their proper coördination is maintained The great importance of roentgenology is stressed but extremists please note these sentences. "Some roentgenologists are of the opinion that the acuteness of the infection and the activity of the lesion may be judged by the roentgen-ray plate. We feel that although a careful study of the film may help in determining a decision as to this, this important question should in the main be based on clinical signs and symptoms." The

chapters on treatment also show a due sense of proportion. Those on collapse therapy, a hard subject to condense, are excellent.

There is an uncommon lot of good practical common sense throughout. Essentials are stressed and unnecessary frills avoided. One or two illustrations will serve to illustrate this. For instance, " . . . in many cases of bronchiectasis the diagnosis is clear, so that the use of lipiodol, at best a disagreeable procedure and not entirely devoid of risk, may well be omitted." That this advice is given in the interest of the patient and not in advocacy of any lack of thoroughness the sentence immediately following in the text makes clear. "Repeated examinations of the sputum by concentration methods and repeated roentgen-rays taken before and after postural drainage will help." And again, "Do not waste time over nonessentials. Much time has been wasted, for instance, in percussing out the narrow strip of normal resonance known as Kroenig's isthmus. From this certain things were deduced and usually wrongly. Likewise before the development of roentgen-ray technique, it was considered necessary to percuss out the excursion of the bases behind. At present with roentgen-ray, and especially fluoroscopic examination available in almost every instance this is a waste of time and energy." Surely this is good "horse sense." On the other hand, in the same connection exception might be taken to the following statement a few pages later. "*Do not* look at the roentgen-ray film or read a roentgen-ray report of the lungs until you have finished your own clinical examination of the chest and have recorded your findings." This is excellent advice if meant for the medical student or for the practitioner endeavoring to perfect his technique of physical examination and for such also percussion of Kroenig's isthmus or of the basal excursion may be a valuable exercise. But to the trained and busy examiner it would seem just as logical and on many occasions less time-consuming to check up his X-ray findings by his physical examination as *vice versa*. However, there are very few statements in the book that anyone acquainted with tuberculosis work could take exception to. The authors are not extremists in any sense and there is an admirable absence of radical or arbitrary views. Perhaps there is a tinge of the latter in this, however. "If by the time you examine the patient the sputum is positive someone is to blame," (either patient or previous physician). This may be an ideal for the future when public health control is so extended or the populace so educated that every individual as a matter of course is periodically examined, but the statement seems a little strong when applied to conditions at present. But for one such sentence a hundred others might be quoted to show the balance and good sense of the book.

The medical student, the general practitioner or the tuberculosis specialist who wishes a short, authoritative and common sense presentation of present views on the clinical aspects of pulmonary tuberculosis will find it in this book.

A short introduction by Dr. R. C. Cabot ends with the following words in which I heartily concur. "Altogether I believe Dr. Hawes and Dr. Stone have given the general practitioner exactly what he needs, a concise, sensible, expert book on a subject of great importance."

FELICE PARODI: *Il Pneumotorace Controlaterale primario di Maurizio Ascoli. Pp. 225, A. Wassermann, Milano, Italy, paper, 30 lire.*

By GEORGE W. WEBER

For a quarter of a century Maurizio Ascoli has been the inspired high priest of the principle of hypotension in collapse therapy. He first began to advocate and practice it in 1912 when he proposed simultaneous bilateral pneumothorax at low pressures, thus opening a new era in the practice of pulmonary collapse. Since 1929 he has gone still further by applying pneumothorax to the contralateral healthy lung in those cases in which a pleural symphysis prevents collapse of the diseased side, calling this new procedure "primary contralateral pneumothorax." His reasoning is as follows: During the course of a usual pneumothorax, the contralateral lung, if already infected, very often shows decided improvement and even complete recovery. He rejects, as being contradictory to the basic idea of pneumothorax, Forlanini's explanation that this might be due to vicarious increase of activity. In his opinion, the improvement takes place only because the contralateral lung is reduced in volume, as demonstrated by Epifanio, and consequently becomes functionally less active. Furthermore, the modifications of the intrapleural pressures of one side are also transmitted to the other side. Parodi, Bordet and others had already found this to be true in unilateral and bilateral pneumothorax. Ascoli, on these premises, considers the lungs in the pleural cavities not as two separate organs, independent from each other, but as one unit which reacts uniformly as a whole to any change of pressure exerted upon one of its sides. In other words, the pneumothorax he proposes will release the elastic tension and reduce the functional activity of the contralateral lung in the same way, although in a lesser and variable degree, according to the mobility of the mediastinum, that it releases the elastic tension and reduces the functional activity of the homolateral lung. The only elements necessary for its success are an entirely free pleural space on the good side and a fairly movable mediastinum. Its management is the same as that of a homolateral hypotensive pneumothorax. The final pressures must produce a bilateral release of tension with a corresponding decrease of functional activity, which will be at the expense of the air reserve, without eliciting at the same time vicarious compensatory reactions. The "threshold of pressure" should be between the extremes of -4 $+2$ in expiration.

Parodi's understanding of the mechanism of action of such pneumothorax

is quite at variance with Ascoli's. His contention is that the mechanical actions and reactions induced by collapsing one lung are transmitted to the other lung not through the mediastinum, but by the variations of tension which, as a result, take place in the bronchial trees. Unfortunately, it is not possible in this short review to go into the details of his theory, which, though interesting and plausible in parts, is, in my opinion, vitiated by the excessive importance he attributes to the weight of the lung in the production of intrapulmonary tension. Consequently, his judgment is also biased when he states that the deviation of the mediastinum, being the result and not the cause of the hypotension produced in the uncollapsed lung, which is true, is not essential to the ends of the treatment. Yet, how can an effective hypotension take place unless some tissues give way? The bronchial relaxation seems hardly sufficient.

Another major point of disagreement between the two authors is the volumetric change in the uncollapsed lung. While Ascoli maintains that its volume decreases, the contrary is believed by Parodi. In his opinion, the uncollapsed lung undergoes greater expansion the moment that the resistances to its distension by the opposite lung are abolished when the latter is collapsed.

It is evident that Parodi's conception is more complex and, perhaps for this same reason, less clear and convincing. However, the discrepancies are more theoretical than practical and they cannot involve such differences in technique as Parodi seems to believe. Pleural pressures and pleural gaseous interchanges being what they are, no lung could be kept within definite and narrow limits of collapse for any length of time. Of importance is the fact that they agree on the basic principle of hypotension.

Needless to say, the application of the primary contralateral pneumothorax is one of necessity and not of choice. First devised to treat unilateral lesions only, its indications have lately been extended to include bilateral lesions, in which case the pneumothorax is applied to the less diseased lung, always provided that the pleural space of the more diseased one is obliterated. It may also be used to render more effective other surgical procedures such as phrenic interruptions and partial thoracoplasties. The lesions which will best benefit from it are of the exudative or fibrocaseous type with tendency to retraction, located in the upper portion of the upper lobes.

This additional indication of pneumothorax therapy proposed by Ascoli is based upon sound principles, but whether it will be accepted and widely applied is doubtful. The idea that hypotension is sufficient to create in the lung conditions apt to stimulate the reparative processes of tuberculous lesions is still too foreign to many. It may be expected, therefore, that primary contralateral pneumothorax will have, like its older brother, the simultaneous bilateral pneumothorax, to overcome a good deal of scepticism and opposition before being allowed to join the ever increasing family of collapse therapy.

PR. HOVELACQUE, OLIVIER MONOD, AND HENRI EVRARD: *Le thorax, anatomie médico-chirurgicale. With 125 plates and diagrams designed by A. Moreaux, pp. 356, Paris, Librairie Maloine, 1937, paper.*

By ADRIAN A. EHLER

Almost inevitably one approaches each new anatomy book with mixed feelings of reverence and weariness engendered by a lack of expectation. Many years have cast a hallowed adumbration on the subject. Seemingly the facts remain static and the efforts of successive authors are directed to a reëxposition of these facts. In general this book has turned rearranged lights upon the anatomy of the thorax, bringing into sharper focus some points and allowing others to remain in the penumbral zone. By title and by intent (as expounded in a modest introduction) the authors have written an anatomy book to provide the thoracic surgeon and internist with a satisfactory and rather meticulous view of the region in which they work.

Foremost in the minds of the authors is the thought of the development and expansion of thoracic surgery. With this in mind they have presented the surgeon with a book that brings into the light the practical and useful knowledge of the thorax and its contents. Naturally with this in view some anatomical points have been treated rather slightingly. Hence, because of its importance in surgery, the phrenic nerve, its abnormalities, and its variations, have been thoroughly and lucidly described in six pages supported by excellent drawings. On the other hand the vagus nerve has been rather summarily dismissed. But there can be no quarrel with that shift of focus.

In a conventional fashion the authors have divided the book into four parts. The first is devoted to the descriptive anatomy of the thoracic wall. Even in this basic section the emphasis has been placed on answers to the question, "But how does this anatomy affect the course of disease or one's surgical efforts?" To provide a satisfactory answer the authors have stressed the importance of these structures in regard to their thoracic relations. Thus one finds the *latissimus dorsi* and *serratus magnus* muscles described as accessory muscles of respiration. It is assumed that the persons who will find this book useful will already have acquired a fundamental knowledge of anatomy.

In the second section there is the descriptive anatomy of organs contained in the thorax. Particularly satisfying is the description of the intrapulmonary ramifications of the bronchi—a controversial subject on which several views have been presented. The remaining organs are described with uniform excellence.

The third and fourth sections contain the topographical anatomy of the thoracic wall and contents respectively. In preparing these sections the authors have dissected many cadavers and have also made full use of clinical examination of living patients and roentgenograms. The result is a clear

projection of the thorax. Because the book has been written for the surgeon and internist there is much in it that has been slurred or skipped entirely in the older anatomies. The anatomy of the pleural dome with its suspensory apparatus of connective tissue, ligaments, and aponeurotic attachments, is outlined in a lucid fashion. There is a very good description of the mediastinum and the triangular ligaments. In describing the pulmonary pedicles the authors have chosen to peer at anatomy between the blades of retractors. However, this is not a book of operative surgery nor is it a conventional surgical anatomy. (The authors have in preparation a volume of truly surgical anatomy.) In this volume anatomy is not described as it appears through classical operative incisions.

It is too bad that the credit given to other authors is so superficial. There is no bibliography; many apparent authorities are cited by parenthetical inclusion of their names without mention of when their work was done or where it may be found.

The format and typography of the book are worthy of compliment. There are also excellent illustrative drawings and diagrams. In short, the book is a commendable presentation of thoracic anatomy; it is meant to be, and should prove to be, useful to the practitioner in thoracic medicine and surgery. Even considered as anatomy, unadulterated by the practical, it compares most favorably with the many volumes that have passed through numerous editions and revisions.

A. L. PUNCH AND F. A. KNOTT: *Modern treatment of diseases of the respiratory system. With 96 plates and 31 figures in the text, pp. viii, + 289, P. Blakiston's Son & Co., Inc., Philadelphia, 1936, cloth, $5.00.*

By FREDERICK BECK

Although written principally for the general practitioner and the senior medical student, this book is nevertheless a brief and valuable guide for the internist treating respiratory diseases.

The subject matter treated ranges from the milder forms of respiratory diseases, such as the common cold and other acute upper respiratory infections, through the diseases of the lungs, bronchi, and pleura, including bronchiectasis, bronchial asthma, the pneumonias, abscesses, tuberculosis and tumors. The differential diagnosis, symptomatology and treatment of these conditions are briefly discussed. Diagnostic and therapeutic procedures such as the injection of iodized oil into the bronchial tree, aspiration of fluid from the pleural cavity, pleural lavage, blood transfusion, pneumococcus typing, and artificial pneumothorax are completely described and discussed as regards their techniques and indications, and are well amplified by diagrams. The discussions concerning the diagnosis, management and therapy of bronchiectasis, pul-

monary neoplasms and tuberculosis of the lungs are particularly outstanding and complete in regard to present methods of treatment. The reproductions of the roentgenograms to illustrate these conditions are excellent.

While the authors must be dogmatic in such a brief treatise, their views are predominantly conservative and sound. Their faith, however, in the prophylactic use of vaccines in upper respiratory infections and in the pneumonias is probably too enthusiastic.

It is unfortunate that the briefness of the book precluded the inclusion of a bibliography as a supplement to the text; but it is nevertheless a concise and thorough guide to a rational method of the management of respiratory diseases.

EMILIANO ELZAGUIRRE: *La Primo-Infeccion Tuberculosa. Pp. 380, Liberia International, San Sebastian, 1934, cloth.*

By FRIEDRICH G. KAUTZ

The author, who previously contributed to the Spanish medical literature valuable books concerning pulmonary surgery and a general book on pulmonary tuberculosis, presents in the present monograph the results of a comprehensive study of two hundred cases of primary tuberculosis of the lung. The cases came under his observation in the course of three years at the Tuberculosis Hospital and Dispensary of San Sebastian. With the contributory work of a large staff of coworkers and pupils the author's book is devoted to all the problems which arise from an anatomical and clinical viewpoint. They are treated in a broad and ample manner with a critical analysis of the modern concepts of the world literature. In the first introductory chapters the questions of epidemiology, heredity, contact and their medical and social importance, chiefly in relation to the incidence and fatality of pulmonary tuberculosis in Spain, are discussed. The author outlines the difficulties of an early and exact diagnosis and therefore emphasizes the necessity of a close collaboration between the phthisiologist and the pediatrician and the family physician. Short chapters providing necessary and clear-cut outlines of the fundamental problems of phthisiology are masterpieces of conciseness. A large part of the volume is devoted to the primary infection and its intrathoracic lymphatic reactions. The author describes his concept of the occurrence and development of primary tuberculosis; he emphasizes the necessity not to refer in the question of the evolution of an areated pulmonary lesion to the results following the injection of large doses of tubercle bacilli in animal experiments. The development and course of a primary focus which have occasionally been observed in children show that the alveolar lesion and the consecutive tissue and lymphatic reactions are different from animal experiments: they may be misleading in their application to human pathology. If there is any similarity in the course of the reactions this can be shown experi-

mentally with a small dose of not more than .001 mgm. These basic observations of the tissue reaction allow conclusions as to the period of incubation, of the primary course and eventually of a prognosis. The clinical discussion is devoted to the various localizations and is aided by many informative illustrations. Later chapters describe the lymphatic reaction, and here the author presents anatomical postmortem findings. Finishing with the outlining of the clinical syndrome of the primary infection and its regression, the author passes over to the secondary manifestations, describing the diagnostic value of the cutaneous tests, of the eruptive skin lesions and their differential diagnostic distinction, and of the primary phthisis with and without miliary tuberculosis. In brief chapters the prevalent problems of therapeutic procedures are dealt with, complemented by interesting statistics concerning the prophylaxis with BCG. The material offered also many occasions to observe the complications involving the pleura and the pericardium, and the lesions were studied in relation to their lymphogenic origin. These conditions are further explained in an ample manner by X-ray pictures and anatomical drawings. The book is an elaborate piece of research work based on a relatively small material; the intensive study of the cases, their critical examination and the habit of the author to refer to the most modern concept concerning the problems at hand, make this monograph a work of high standard

AGOSTINO CURTI: *Le Lobiti Tisiogene. Pp. vi + 130, Milano, Tipografia Enrico Zerboni, January 20, 1934, paper.*

By FRIEDRICH G. KAUTZ

According to Bernard a tuberculous lobitis (lobar tuberculosis) is the involvement of at least one whole lobe. The rich material of the Ospedale Sanatoriale in Vialba offered the opportunity to select over one hundred cases which presented the clinical and roentgenological appearance of lobar tuberculosis. In brief chapters the anatomical and aetiological foundations are discussed. As compared with the relative age at the onset of pulmonary tuberculosis in general in the adult, there is a marked increase in frequency between the ages of 21 and 30 years in the development of lobar involvement. This age-group represents nearly 50 per cent of all the cases. While the involvement of the right upper lobe is by far the most frequent, the left upper lobe is affected only exceptionally. Of 106 cases of tuberculous lobitis there were 101 in the right upper lobe, only one in the left side, and four cases were in the right middle lobe. The average frequency of left-sided lesion differs somewhat from previous statistics in the literature amounting to 3.5 per cent. The chapter on the pathogenesis maps out the aetiological importance of inhalation, of endogenous reinfection by the bronchi and the hilar lymph nodes. This latter source of infection is represented by simple and hyperplastic hilar lymph-

adenitis and leads, by the way of ganglio-pulmonary or interlobar ganglio-hilar propagation, to interlobar and peri-interlobar tuberculous lesions. The chapter closes with a brief outline of haematogenous spread and with interesting remarks on the influence of anatomcal-functional considerations. Many pages and illustrations are devoted to the radiological and clinical appearance which are supplemented by short clinical reports of 106 cases. Diagnosis, prognosis, and therapy and their results, including collapse therapy, are described. The author gives adequate and somewhat more detailed information about the fate of the patients during a period of one year and more following the beginning of the treatment. Many schematic and roentgenological illustrations explain the text. The make-up of the book is indicative of the high level of modern Italian scientific literature.

ED. WERDENBERG: *Beurteilung und Behandlung der Augentuberkulose. Beiageheft zu Montasblätter für Augenheilkunde, vol. 95, Ferdinand Enke, Stuttgard, Germany, 1935.*

By HERMAN ELWYN

Werdenberg begins his discussion by tracing the development of our knowledge of tuberculosis of the eye. He outlines four stages: (1) a pathologico-anatomical stage, beginning with v. Michel; (2) a stage of experimental investigation, beginning with Cohnheim; (3) a stage of investigation into the primary focus of tuberculosis, based on the work of Axenfeld and de la Camp; and (4) a stage based on the fundamental work of Ranke, in which there has evolved our understanding of the relation of tuberculosis of the eye to the general tuberculosis infection of the body. The various phases in the course of tuberculosis correspond to the three stages of development according to Ranke.

Although the manifestations of ocular tuberculosis belong to Ranke's secondary stage, that of general dissemination, they show, nevertheless, early secondary, secondary, and late secondary forms. The type more closely related to Ranke's primary stage, with its normal reaction of the organism toward tuberculosis infection, is the early nodular tuberculosis of the iris, a juvenile form of tuberculosis. The type occurring in the secondary, hypersensitive period, is the diffuse plastic exudative iritis of puberty and the postpuberty period. Corresponding to the tertiary, partially immune, period, is the late secondary productive fibrous tuberculosis, occurring especially in advancing years. A special place in the scheme of tuberculous infection must be given to the juvenile retinal periphlebitis, the haemorrhagic form of ocular tuberculosis.

Clinically, the diagnosis and treatment of tuberculosis of the eye is dependent upon a proper understanding (1) of the characteristics of the various forms of tuberculosis of the eye; (2) of the intrathoracic source of infection; and (3) of the general tuberculous infection of the body.

Werdenberg finds three main forms, the exudative, the productive and the fibrous. When the several forms occur together, one usually predominates. The exudative is the more malignant "toxin-sensitive" form. The productive and fibrous are the less sensitive and more benign forms. This distinction also influences the specific treatment, tuberculin being indicated in the productive and fibrous forms and contraindicated in the exudative form.

There is a certain antagonism between ocular tuberculosis and intrathoracic tuberculosis. Werdenberg calls this a normal antagonism when there is severe ocular tuberculosis with slight intrathoracic findings. In 500 cases in which roentgen films of the lungs were studied this normal antagonism was found in 60 per cent. As an inverse antagonism Werdenberg characterizes the presence of a mild tuberculosis of the eye with severe pulmonary tuberculosis. This he found in 10 per cent.

Toxic symptoms of general tuberculous infection are more frequently ob served in the exudative than in the proliferative and fibrous forms, but frequently there is no relationship between the particular form and the toxic symptoms. Treatment must also take into consideration the general infection.

The diagnosis of tuberculosis of the eye is, strictly speaking, a probability diagnosis, depending upon the clinical picture in association with the physical and roentgenological examination of the chest. A positive tuberculin test helps, but a negative test does not necessarily exclude it.

The treatment of tuberculosis of the eye is general and local, and has three points of attack: (1) the organism as a whole, (2) the tuberculous focus in the body, and (3) the eye. Treatment of the organism as a whole is a constitutional one and involves an attempt to change the immunobiological reaction of the organism to the infection (Umstimmung). This is accomplished by climatic treatment and by means of tuberculin. The latter involves strict indication for its application and proper dosage. It should not be schematic but according to the individual need. Werdenberg uses Sahli's subepidermal method. He divides the tuberculins according to their toxicity: (1) slight toxicity, Rosenbach's sensitized bacillary emulsion; (2) immunizing action with moderate toxicity, Koch's bacillary emulsion, Béranek, Tebeprotein; (3) toxic action, Old Tuberculins, A.T.O., A.T.; the latter is the most toxic.

In the final chapter, Werdenberg gives his statistical results. He has treated 1,100 cases of ocular tuberculosis. Of these the uveal tract was involved in 85 per cent of the cases, with iridocyclitis in 65 per cent and choroiditis in 20 per cent. Puberty and climacterium are the most frequent periods of life for the occurrence of ocular tuberculosis.

The 33 page pamphlet presents a short and concise review of the present conception of tuberculosis of the eye by one who has had a large experience. It is, perhaps, too short and too summary, but it is well worth a closer scrutiny.

CHARLES LE SÉAC'H: *L'Image granitée post-hémoptoique. (Etude clinique et pathogénique.) With 13 figures in the text, pp. 141, Librairie Louis Arnette, Paris, 1936, paper.*

By J. BURNS AMBERSON, JR.

The subject of this monograph has to do with the finely mottled or studded, hence "granitic," appearance of the roentgenograph of the lungs of a tuberculous patient after he has had one or more haemoptyses. "Granitic" is a good descriptive term, indicating a grainy or granular type of shadows. All are familiar with the picture which may represent an acute posthaemorrhagic development going on to caseous pneumonia, resolving almost completely or leaving behind the small round densities which persist indefinitely or undergo fibrous transformation. In this country the shadows are usually taken to represent a dissemination of tuberculous lesions from the aspiration of blood laden with tubercle bacilli, though a few have explained them on the basis of atelectasis. Séac'h considers in detail the clinical and experimental evidence presented by Austrian and Willis and the reviewer in the early 1920's, and argues that the conclusions were wrong that the changes are specifically due to bacillary infection. Likewise, he opposes the atelectasis theory. His conclusion is that the shadows represent exudation in the lung and that this is caused by the same thing as the haemorrhage, namely, a disturbance of the "neurovegetative equilibrium." An interesting discussion draws attention to the nervous regulation of pulmonary function, an important mechanism barely known to most of us. Nevertheless, the author is not able to adduce much objective evidence for his hypothesis, and leaves it as such. More recent American work has provided strong evidence from clinical and postmortem examination that the former interpretation of these shadows is the correct one. Incidentally the book includes a careful analysis of the clinical features of haemoptyses. An unusual literary feature is the dedication. Thirty-seven persons are specifically named for this honor, besides numerous others included in groups.

ETIENNE BERTHET: *Rôle des Voies Lymphatiques dans la Génèse de la Tuberculose Pulmonaire, leurs rapports avec la tuberculose pulmonaire interstitielle. With a preface by Professor Sergent. With 12 illustrations, pp. xii + 98, Paris, G. Doin & Cie, 1936, paper, 20 fr.*

By MAX PINNER

The apparent and real puzzles presented by the pathogenesis and epidemiology of tuberculosis stimulate once in a while an attempt at a revolution against what appears to be well established fundamentals. The present monograph

is such a revolution, or probably more correctly a revolt, since the scope of the attack is rather slender in comparison with the broad basis that is assailed. The argumentation proceeds in orderly and logical fashion step by step, but the basis of each step seems narrow and tenuous.

It is well worth while to follow Doctor Berthet through his reasoning, step by step, armed with all the critical reserve that the importance of his subject deserves. Doctor Berthet first states that the primary complex as elaborated by Parrot, Küss, Ghon, Ranke is not a reliable indicator for the portal of entrance of tubercle bacilli. First, because according to Calmette bacilli cannot reach the lower air-passages with the inspired air under physiological conditions; this is deemed satisfactorily proven by the fact that the alveolar air is always found to be sterile. But since coal and siliceous dust find apparently easy access to the pulmonary parenchyma it needs probably more than an authoritative citation to settle this question. Secondly, it is stated that the anatomical and histological characteristics of the primary complex do not permit of a distinction from other, that is, reinfection foci. This argument appears inviting only by virtue of the totally inadequate description that is presented of the primary complex; it is deplorable that Doctor Berthet does not mention in this connection the fundamentally important work of such authors as Schürmann and Blacklock, but only casuistic reports of apparently absent or atypical primaries. While negative findings *per se* are less convincing than positive ones, it should at least be demanded that negative results be based on equally painstaking search as those that yielded positive results. For this reason, all merely clinical and roentgenological reports of absent primary foci attest only to the inferiority of the methods employed. Doctor Berthet puts much weight on the well known fact that pulmonary lesions may be produced by bacilli deposited anywhere within the body; but it still has to be shown that by any other than local administration, a focal pulmonary lesion with the characteristics of a primary complex can be induced.

The next chapter reopens the old discussion of anastomoses between the cervical and mediastinal lymphatic chains. Since it is admitted that such anastomoses exist, if at all, only in exceptional cases under normal conditions, emphasis is put on the clinical necessity of assuming such connections following inflammatory alterations. However, every pathologist has seen cases in which both lymphatic systems were involved by tuberculosis. It is, then, always found that in terms of massiveness of involvement, the two systems form two pyramids, the cervical with a superior, the mediastinal with an inferior broad base, and the apices of the pyramids meeting somewhere near the borderline of the two regions. This is an impressive and convincing argument for the independence of these two regions of lymphatic drainage.

The frequency of tonsillar involvement, presented as argument for the assumption that tubercle bacilli enter frequently through these organs, is no

criterion, since practically all, if not all, reports cited are based on the examination of biopsy specimens without any evidence that the tonsillar lesions were the only, or at least, the apparently oldest foci.

For similar reasons, the clinical reconstruction of cutaneous primary infection from the neck—made invitingly possible by actual or assumed impetiginous lesions—cannot be given serious weight.

A group of 14 patients is presented with calcified cervical lymph nodes and homolateral pulmonary tuberculosis in support of the author's view of direct lymphatic drainage from the cervical region into the pulmonary parenchyma. Since Doctor Berthet declines to accept the pathologico-anatomical evidence for the reconstruction of a chain of developments, the same criticism ought to be applied to roentgenological evidence.

Doctor Berthet concludes that a frequent mode of primary infection is through the upper respiratory organs and the skin of the neck; that, at least under pathological conditions, lymphatic drainage from the cervical to the mediastinal lymph nodes and hence to the pulmonary parenchyma occurs; that direct aerogenous infection of pulmonary tissue is impossible; and that bacilli entering through lymphatic tissue are so deprived of their virulence that, reaching the lung, they produce benign, interstitial lesions. We are not told, however, how those bacilli enter the lung that cause rapidly destructive phthisis.

It was not necessary in the reviewer's opinion to prove again that tubercle bacilli may enter the lung by other but the aerogeneous route; we are all agreed on that. In support of the author's contention, it was necessary to prove that bacilli entering through the portals favored by him, can produce a lesion in the lung resembling a primary complex. This proof has not been attempted.

Doctor Berthet's monograph is an interesting and somewhat impatient and breathless study; it is based more on selected literature and circumstantial evidence than on direct observation. It seems, therefore, unconvincing, probably even to those readers who need not plead as definite a preconceived bias as this reviewer.

D. B. CRUICKSHANK: *Tuberculosis, cancer and zinc, an hypothesis. With an introduction by Sir Pendrill Varrier-Jones. With 26 tables, pp. xv + 75, London, Medical Publications, Ltd., 1936, cloth, 7/6.*

By MAX PINNER

If one is confronted with a thesis that promises to explain in a satisfactory manner some of the major problems of the pathogenesis and epidemiology not only of tuberculosis but of cancer as well, if at the same time such a thesis is sufficiently far removed from the well worn (and possibly well tested) ideas

that may sometimes appear stale by familiarity and routine and not too encouraging by their demonstrable achievements, if such a thesis is presented with the unassuming charm of the rather serious causeur and not with the ponderous zeal of the messiah of an epochal thought, then, the reader's aesthetic sensibilities are in danger to be more acutely affected than his critical sensitivity. And so, it is with mellowness, rather than with acuity that one is apt to think of Doctor Cruickshank's book. But this reviewer's mental reaction to the book is totally insignificant lest it be accepted as a broad apology for the evasion of his obvious duty: a critical review. Instead he will present in barest outline the chain of thought of Doctor Cruickshank's hypothesis, and hypothesis it is called by its author, and hypothesis appears in large fat print.

The decline in the tuberculosis mortality rate, obviously out of gear with all organized efforts to combat the disease, shows chronologically and quantitatively a close parallelism with the appearance and diffusion of available zinc in human environment (notably by the instrumentality of the zinc-lined milk pail). Further circumstantial evidence, such as the geographical distribution of tuberculosis-resistant animals in zinciferous regions, supports the idea that zinc increases the resistance to tuberculosis.

The sum of the tuberculosis and cancer death-rates has remained constant for long periods, and the reciprocal relation of the two diseases is further suggested by the relative tuberculosis-resistance of cancer-susceptible animals and *vice versa*. While tuberculosis seems to be associated with a hypo-zinc state, the reverse is true of cancer. The combined mortality of tuberculosis and cancer is constantly 20 per cent of the total mortality (in England). The exactly antagonistic statistical behavior of the two diseases can only be explained if it can be shown that the growth of one disease prevents the development of the other. "In the 20 per cent group, who alone are susceptible to those two diseases, the decision as to which disease will ultimately cause death is made at the moment of (or *circum* the moment of) infection by the tubercle bacillus." This statistical postulate is fulfilled by the assumption that the bacteriophage specific for the tubercle bacillus is the virus causing cancer. It is now simple enough: as long as the Janus-faced phage is engaged in his battle with the tubercle bacillus, his carcinogenic propensities remain in abeyance; when the battle is won, his neoplastic function is set free.

As far as I can see, Doctor Cruickshank's hypothesis is original. The historical evaluation of bold theorists, like that of bold revolutionaries, is decided by their success. In the absence of material facts it is perilous to attempt a prophesy. But it may be in order to point out the absence of material facts, save some statistical correlations. The statistically assumed influence of zinc on tuberculosis and cancer is unproven, but susceptible to experimental verification. With the incidence of tuberculosis infection which is much higher

than 20 per cent, many a phage-bacillus battle must end in the stale mate of mutual exhaustion, especially since cancer does not appear to be particularly frequent in patients recovered from tuberculosis; this is a point that is not mentioned. The assumption of an antibacterial carcinogenic phage must have originated in Doctor Cruickshank's mind long before Steencken, shortly before the publication of Doctor Cruickshank's book, presented incomplete but suggestive evidence for the occurrence of a tubercle-bacillus phage. If this does exist, its neoplastic qualities must still be shown. Doctor Cruickshank has evaded meticulously and wisely the arguments in the discussion of the infectious nature of cancer.

In brief, it is, generously seen, probably true that, using what Doctor Cruickshank himself calls "diffuse logic," this hypothesis is not contradicted by any known fact *eo ipso*; but it is probably equally true, that none, but rather vague and statistically derived observations, are available at present to support it.

FRED H. HEISE: *1000 Questions and answers on T.B. Journal of the Outdoor Life, New York City, 1935, pp. vi + 232, cloth, $.75.*

By CHARLES W. MILLS

The Journal of the Outdoor Life, during most of its existence, maintained a Questions and Answers Department. Doctor Heise conducted this department for twenty years and the book under discussion is a selection and compilation from these questions and answers. An attempt has been made to select those questions about tuberculosis which, from the frequency of their appearance, seem to be uppermost in the minds of patients. The questions are classified and arranged under a number of titles and subtitles in an effort to secure sequence and for ease of reference.

The answers are almost without exception excellent. The task of answering such questions must be difficult. Besides a thorough knowledge of the subject, in this case tuberculosis, especially in its bedside aspects, it would appear to require a considerable amount of tact as well as cleverness. A physician answering a question from a patient whom he has never seen, and about whom he knows nothing except for the small amount of information furnished by the question, needs both cleverness and tact if he is to give an answer that will enlighten and satisfy the questioner and at the same time not lead him into harm by attempted self-treatment and not trespass on the proper field of his attending physician. Doctor Heise appears invariably in his answers to have this necessary cleverness and tact. His thorough knowledge of tuberculosis enables him to give sensible and helpful answers and he shows an uncanny ability to avoid pitfalls.

The question-and-answer form is inherently a poorly adapted form in which

to cast subject matter intended for consecutive reading. The effect is necessarily broken and choppy and sustained interest hindered. It must be said, however, that Doctor Heise by means of the sequential arrangement of the questions has succeeded fairly well in overcoming this inherent limitation, and that the book is not uninteresting when read as a consecutive presentation of the subject. Perhaps it is better classified, however, as a very excellent reference book on tuberculosis for patients.

I. S. FALK: *Security against sickness, a study of health insurance, America's next problem in social security. Pp. xii + 423, Garden City, New York, Doubleday Doran and Company, Inc., 1936, cloth, $4.00.*

By BERNA RUDOVIC PINNER

This is a comprehensive groundwork for planning a program of health insurance for the United States. The material gathered by the Committee on the Costs of Medical Care is used in the analysis of the situation here; and the marked differences in opinion between members of this Committee, on some issues, of which so much point has been made by interested persons and organizations, are shown to be slight in comparison with their essential agreement. The case for the necessity of a program of health insurance is made out convincingly. The author points out the anomaly of inadequately employed physicians and nurses coexisting with a laity in need of their services. The average individual's expenditure yearly for medical care is well under thirty dollars; but medical care differs from any of the other necessities of life in being unbudgetable. No amount of living-within-one's-means can give one security against an illness, the costs of which may exceed annual income, and when it strikes the breadwinner, may at the same time wipe out the income. In the intervals between depressions, one-third to one-half of all cases of family dependence have their genesis in sickness and its economic sequelae.

Four European systems of insurance against sickness are investigated: the German, the British, the French and the Danish. The German system, by far the oldest, has undergone considerable changes. At the time it was instituted, the bulk of insurance relief was compensation for loss of wages due to incapacitating sickness; now medical service is the primary benefit. The British system has existed nationally since 1911; the government took over the system under which private "Friendly Societies" had long been operating. France, also, before the adoption in 1930 of her national law on social insurance, had long experience with voluntary and private associations for sickness insurance. The French system is notable for the large part which physicians had in dictating its terms. There, the physician is paid by the patient, who is reimbursed (up to 85 per cent) by his insurance fund. The system in Denmark is nominally voluntary, but social and economic pressure makes it in effect compulsory.

All four of these systems include only people in the lowest economic brackets. The author feels it to be desirable to cover also classes higher in the economic scale.

The relative merits of voluntary and compulsory insurance are studied exhaustively. There is really no purely voluntary and modern system in existence. The author—in contradistinction to the majority of the Committee on the Costs of Medical Care, which felt that the State was not justified in compelling payment of funds until there could be an equivalent guarantee for adequate service—says "Instead of organizing for the payment of medical costs after having achieved improvement of service, society must organize for payment in order to achieve improvement of service."

The last chapter, *Some Basic Principles for an American Program*, is an excellent and even masterly summation.

Patologia Comparata della Tubercolosi, April 28, 1935, vol. 1, no. 1, (*A cura dell' Istituto Vaccinogeno Antitubercolare*, Director: Prof. Alberto Ascoli). (*Supplemento della Rivista Biochimica e Terapia Sperimentale.*)

By FLORENCE R. SABIN

We have been asked to review a new Italian journal on tuberculosis, in order to introduce it to the American medical public. The first number of this Journal of Comparative Pathology of Tuberculosis, edited by Professor Alberto Ascoli and published under the auspices of the Istituto Vaccinogeno Antitubercolare, appeared on the 28th of April, 1935. It is devoted almost exclusively to the subject of vaccination with the Bacillus Calmette-Guérin.

The first article, entitled *Esperimenti di raffronto vaccinale*, is an account of the preliminary experiment on the "vaccinal antitubercular comparison" performed by the Istituto Vaccinogeno Antitubercolare at Guinzano. It describes the vaccination of one calf at birth with 50 mgm. of BCG subcutaneously, and of a second intravenously with 500 mgm. of a virulent heat-killed bovine organism. These two calves were then inoculated with 5 mgm. of the same virulent living culture, together with two controls. The calf which had received the BCG showed a high degree of resistance to the subsequent inoculation; the calf which had received the heat-killed organisms developed a spontaneous infection even before it was inoculated; and the controls developed tuberculosis.

The second article, by Dante Pansera, entitled *Azione protettiva del B. C. G. contro la tubercolosi spontanea della cavia*, describes an experiment in which twenty guinea pigs vaccinated with BCG were kept in a pen with twenty pigs which had been inoculated with virulent bovine tubercle bacilli intraperitoneally, and fifteen which had been inoculated with the same strain subcutaneously, and twenty which had neither been vaccinated nor inoculated. The number of cases of spontaneous tuberculosis was followed. Of the normal

controls, eight died of intercurrent infections. The experiment was followed for 10 months; in 8 months, palpable inguinal lymph nodes were found in some of the nonvaccinated group, and by 10 months all of these controls, twelve in number, had tuberculous lesions, proved by transmitting the disease to other guinea pigs. During this time none of the group vaccinated with the BCG developed lesions, proved by the failure to infect other guinea pigs with their lymph nodes. These data are all given in tables.

These two articles cover 38 pages. There then follows a short paper by M. Carpano, entitled *Su di un nuovo metodo di colorazione del bacillo tubercolare*, which gives a procedure for staining tubercle bacilli, consisting in the use of carbol-fuchsin, decolorization with weak sulphuric acid, counterstaining with vesuvina, and subsequent treatment with iodine. This procedure allows a greater analysis of the structure of the bacillus than the usual technique.

More than half of the first *Fascicolo*, 121 pages, is taken up with an extensive bibliography concerning the work with BCG.

Brief Comment

F. J. BENTLEY: *Artificial pneumothorax: experience of the London County Council. Medical Research Council, Special Report Series no. 215. Pp. 94, London, His Majesty's Stationery Office, 1936, paper, 1s, 6d.*

It would be a most interesting task to write a lengthy abstract of this study. But a review of it can have only one aim, and that is to say, in the most emphatic manner: everybody at all interested in pneumothorax treatment must read this work. It contains, more than any other monograph on this subject, a wealth of information on practically all those points in pneumothorax treatment that are of practical interest and that can be expressed statistically. It is eminently a book written *sine ira et studio*. One must ponder over all its many tables; and out of the apparently dry statistical presentation will come a vivid realization of much that is important in indication, prognosis and results, more vivid, and certainly more convincing than mere impressionistic data (of which there is plenty in the literature) and more instructive than the lusty discussions between the adherents and the opponents of the method.

Diseases of the respiratory tract. Clinical Lectures of the Eighth Annual Graduate Fortnight of the New York Academy of Medicine. By 21 contributors, with 56 illustrations, pp. 418, Philadelphia and London, W. B. Saunders Co., 1936, cloth, $5.50.

This collection of papers covers in concise and authoritative essays practically all those morbid conditions of the respiratory tract that offer the most important differential diagnostic problems in tuberculosis work. In addition, there are three papers specifically concerned with tuberculosis. The table of contents is indicative of the field covered: E. H. Pool, Opening remarks; M. A.

Ramirez, The relation of allergy to the diseases of the respiratory tract; A. R. Dochez, Common cold; C. T. Porter, Sinus disease from infancy to old age; C. J. Imperatori, Diseases of the larynx, trachea and main bronchi; C. L. Jackson, Bronchoscopy in relation to diseases of the respiratory tract; J. B. Amberson, Jr., Bronchiectasis; H. T. Chickering, Influenza of the respiratory tract; J. C. Meakins, Chronic pneumonitis; C. H. Smith, Pneumonia in childhood; J. A. Miller, The evolution of pulmonary tuberculosis; A. R. Rich, Immunity in tuberculosis; A. V. S. Lambert, Surgery of tuberculosis of the chest; L. U. Gardner, Pneumoconiosis with particular reference to silicosis and tuberculosis; D. Riesman, Emphysema; H. Lilienthal, Chronic nontuberculous empyema: notes for the physician and the general surgeon; H. Wessler, Abscess and gangrene of the lungs; G. Blumer, Pulmonary thrombosis and embolism; Y. Henderson, Atelectasis, massive collapse, and related postoperative conditions; L. F. Craver, Carcinoma of the lung; H. S. Martland, Diseases of the mediastinum.

A. R. SHANDS: *Handbook of orthopaedic surgery. In collaboration with R. B. Raney. With 169 illustrations, pp. 593, C. V. Mosby Co., St. Louis, 1937, cloth, $5.00.*

This recent book on orthopaedic surgery has been written primarily for the medical student; the text has been divided into twenty-four parts to be readily adaptable to undergraduate curricula. The authors have freely utilized the work of many orthopaedic surgeons and have attempted to set up a guide for study. For its purpose the book should prove useful. The text is clear and has been written with simplicity and candor; the illustrations are excellent and reflect the simplicity of the text. The good selective bibliography will doubtless prove to be useful to the practitioner whose interest in orthopaedic problems requires him to know more about diagnosis and treatment than can be supplied in a book which is little more than a guide to instruction.

FRANK KELLNER: *Die "atypische" Pneumonie, eine klinischröntgenologische und differential-diagnostische Studie, zugleich ein Beitraz zur Frage der "Grippe" und des Frühinfiltrats. With five plates, vol. 6 of Immunität, Allergie und Infektionskrankheiten, pp. 52, München, Verlag der Ärztlichen Rundschau, Otto Gmelin, 1936, paper, R.M. 2.70.*

A brief, but rather thorough discussion of more or less fleeting pulmonary infiltrations, with particular emphasis on their differential diagnostic significance in relation to tuberculous infiltrates.

JOSÉ SILVEIRA: *Questões de Tuberculose. With a preface by Cardoso Fontes, 1. Serie, pp. 242, with many illustrations, Argeu Costa & Cia, Bahia, Brazil, 1936, paper, Rs. 30$000.*

This is a loose collection of papers dealing with various practical problems in the clinic of tuberculosis. As Dr. Cardozo Fontes points out in his preface, the collaborators intend to discuss such matters from a modern point of view. José Silveira devotes three chapters to the discussion of aurotherapy with a number of different gold compounds. Eduardo de Araujo reports on BCG vaccination of 1700 newborn in the city of Bahia. Castro Lima presents the clinical and pathological findings in a case of haematogenous tuberculosis of the larynx. Silveira and Alves discuss the association of asthama and pulmonary tuberculosis. In the final chapter, Silveira and Marback report three patients in whom Horner's syndrome was observed, following alcoholization of the phrenic nerve. The book is well edited, many roentgenograms illustrate the text and a large bibliography is added. The authors succeed well in bringing into a clear relief the various problems arising from clinical observations of pulmonary tuberculosis. The subjects are discussed from a modern point of view and a good account of present-day opinion together with a generous discussion of the observation in a large tuberculosis department are assembled by the collaboration of the various authors.

HEINRICH GERHARTZ: *Multiple Sklerose und Tuberkulose. Tuberkulose-Bibliothek, edited by Franz Redeker and Karl Diehl, No. 58, pp. 48, Johann Ambrosius Barth, Leipzig, 1935, paper, Mk. 4.80.*

This is an elaborate, and possibly a labored attempt to prove that multiple sclerosis is a "metatuberculous disease." The arguments are based largely on the literature and are collected in an ingenious, but sometimes rather farfetched manner. A total of 175 literature references are marshalled in support of the author's thesis. This study is interesting, at times more in its sidelines than in regard to the main argument. The impression of the monograph as a whole is more impressive than convincing, but well worth reading.

HANNES SALMENKALLIO: *Über Die Komplementbindungsreaktion von Witebsky, Klingenstein und Kuhn. Über Ihre Spezifität und Bedeutung, speziell bei Lungentuberkulose. Pp. 106, Acta Societatis Medicorum Fennicae "Duodecim," Ser. A, Tom. xix Fasc. 2, Helsinki, 1936, paper.*

This test was performed on some 1600 blood samples from more than 1300 patients, about half of whom did not have clinical tuberculosis. While the total percentage of positive reactions was not unsatisfactory, only about 28 per cent of patients with minimal lesions yielded positive results. As far as a positive diagnosis is concerned, the old experience is repeated that only in patients with far-advanced lesions is the percentage of positive fixations high enough to be of any diagnostic aid. When, then, a negative reaction is no indication whatsoever to rule out clinical tuberculosis, a positive reaction does not prove clinical tuberculosis, since about 20 per cent of patients with poly-

arthritis, more than 10 per cent of syphilitics and 3 per cent of normals reacted positively. In the present thorough studies with a refined technique and antigen that is supposed to be in a particularly felicitous position between the unavoidable Charybdis of specificity and Scylla of sensitivity, the results remain essentially the same as those with earlier and less elaborate procedures of complement-fixation: encouraging in that group of patients in whom a serological diagnosis is not needed, practically useless in that group in which additional diagnostic help would be welcome.

H. KÜRTEN, Direktor der Medizinischen Poliklinik der Universität Munich: *Zur Diagnostik, Therapie und Prognostik der Lungentuberkulose im Altertum und Mittelalter. Pp. 20, Praktische Tuberkulose-Bücherei, Beihefte Des Deutschen Tuberkulose-Blattes. Herausgegeben von Prof. Dr. Kurt Klare, 14 Heft, Georg Thieme, Leipzig, 1936, paper, R. M. 1.30.*

This is a very brief and rather loose-jointed collection of citations from Hippocratic teachings up to the late Middle Ages, concerning the subject matter mentioned in the title. The occasion for this essay seems to be the author's interest in the teachings about tuberculosis of a municipal physician of Memminger, Ulrich Ellenbog, who wrote a consultant's advice in the year 1480. There is, unfortunately, no reference to the original source. Ellenbog seemed to have been a more shrewd than wise believer in eclecticism without—as far as presented in this study—any original thought.

FRANK HAMMOND KRUSEN: *Light Therapy. With frontispiece and 42 illustrations in the text. Second Edition, revised and enlarged. Pp. xx + 238, Paul B. Hoeber, Inc., New York, 1937, cloth, $3.50.*

The first edition of this book was critically and extensively reviewed in the January, 1934, issue of the *Review* (vol. *29*, no. 1). The entire book has evidently been gone over carefully, much new material has been added, the bibliography more than doubled, and errors and omissions corrected. In particular the chapter on physiology, which in the previous edition was quite inadequate, has been considerably expanded. That a second edition appears indicates that many persons have found Doctor Krusen's work stimulating and helpful, a by no means inconsiderable tribute in the face of a confusing and difficult subject. This new and improved volume, in which Doctor Krusen's infectious and continued enthusiasm everywhere abounds, should prove of greater popularity.

Surgeon Errant, the Life and Writings of William Henry Bucher, 1874–1934. Edited by Emil Bogen. With 45 illustrations, pp. viii + 212, Los Angeles, California, The Angelus Press, 1935, cloth, $2.00.

This book is a collection of autobiographical material of Doctor William Henry

Bucher whose eventful life was crowned by the fruitful work he did in Olive View Sanatorium, of which he was Superintendent from 1921 until his death in 1934. Doctor Emil Bogen has edited the book and prefaced it by a brief biographical sketch. The editorial work is of a high order of reference and excellence, and the entire make-up is beautiful and dignified. The wide professional travels of Doctor Bucher make interesting reading since he was a keen observer and an active physician. Here is much that is of real value to the student of the development in American medicine and of the tuberculosis movement.

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TOMOGRAPHY

With Special Reference to Its Value in the Diagnosis of Pulmonary Lesions

J. B. McDOUGALL[1] AND J. H. CRAWFORD[2]

1. INTRODUCTION

The concept of radiology has widened considerably since the discovery of X-rays by Roentgen in 1895, and the advances made in this subject have been no less than in other branches of medicine and science during this period. The services rendered by radiology to the art of diagnosis are paralleled only by those of anaesthetics and antisepsis for treatment; so much so, that it is impossible to visualise modern medicine, as we know it, without this acquired aid.

Alban Kohler, in the preface to the most recent edition of his monumental book, enumerates twenty subdivisions of the field of radiology, ranging from amniography to venography which he had been compelled to omit from his volume—a striking indication of the remarkable increase in the extent and technique of modern roentgenology. Almost every organ of the body has been brought within the scope of the radiologist, and the advances which have been made in the reproduction of even the finest detail of soft tissues are eloquent testimony to the success of workers in this field.

The particular problem of the chest has always been of some difficulty owing to the presence of the bony structures forming the thoracic cage, and it was as a contribution to the solution of this problem that tomography, that is, the reproduction of layers of the chest, was devised.

2. THEORY OF TOMOGRAPHY

1: Sources of difficulty in the interpretation of a skiagram of the chest: In radiology it is well known that there may occur a diminution in the translucency of normal lung tissue by reason of thick scapulae, well-formed pectoral muscles, the mammary gland in females, or a large thymus gland in children. More important than any of these factors,

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however, is the presence of the ribs, the shadow of which covers about two-thirds of the lungs. This simple fact is not often appreciated. Thus we have a translucent organ, the lung, encircled by much less translucent parts; not only do difficulties of superimposition arise, but for adequate penetration harder rays must be used than those which would be suitable for the lungs themselves.

Further difficulties in the interpretation of the ordinary anteroposterior film of the chest are due to the superimposition of the structures within the lung itself. Shadows of blood-vessels, bronchioles and alveoli are

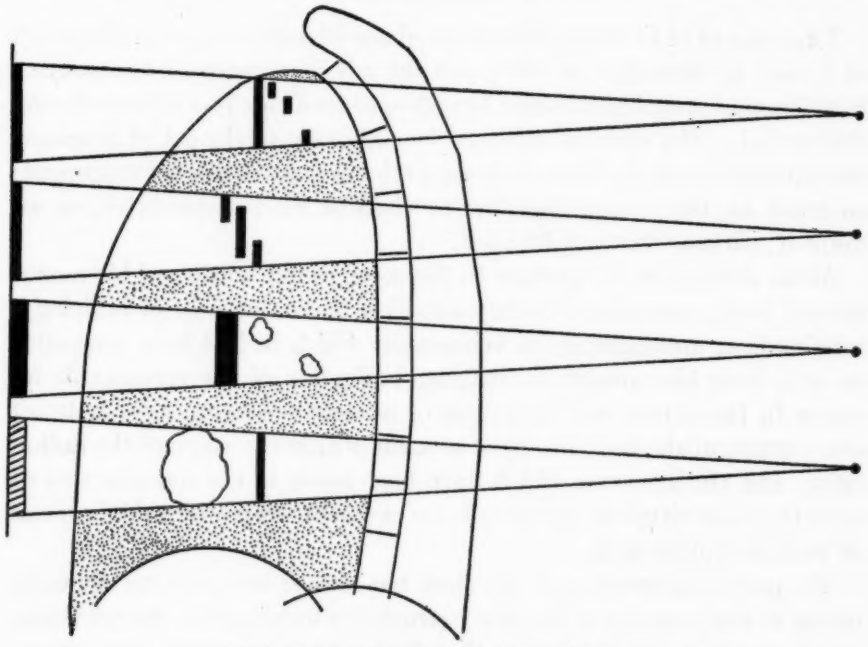


Fig. 1. Showing superimposition of lesions

superimposed, and give rise to sharp contrasts which may be wrongly interpreted as being due to pathological lesions. When one recalls that the usual "flat" film of the chest is simply the product of the shadows of all the structures which lie within the effective cone of rays during the exposure, it becomes evident that the analysis and interpretation of the final picture may often be difficult, and, in some cases, even misleading.

Figure 1 (adapted from Chaoul) gives a simple illustration of the superimposition of foci situated at different depths in the chest; small lesions or structures which lie in the path of the shadow cast by a large, dense

lesion are entirely covered and lost, and in this way it is possible for the shadow of a cavity, for example, to be quite obliterated. Any method, therefore, whereby layers of the chest at previously determined depths can be photographed places at our disposal the means for exact representation of pulmonary lesions, with a consequent gain in accuracy of diagnosis. And as far back as 1921, Bocage attempted, with only limited success, to produce an apparatus which would satisfy these requirements and reproduce a lung-section free from superimposed shadows.

2: Advantages of tomography over stereoscopy: Before going on to a discussion of the geometrical principles of tomography, it may be of value to consider the question of stereoscopy as an aid toward the elucidation of intrapulmonary lesions. We will readily admit that by the use of oblique films, or stereoscopic films, the expert radiologist is often able to obtain a greater degree of differentiation than is possible with the usual dorsoventral picture; but, even so, free and isolated vision of different foci is only produced to a limited degree. Furthermore, the fact that a large number of people cannot see stereoscopically limits its practical value and militates against its wide adoption. The fact has to be recognized that, despite many attempts to stimulate and maintain interest in stereoscopic work, this method of investigation has never been very widely adopted; and it is our experience that tomography reveals with clarity lesions which are difficult to demonstrate by the other methods enumerated above.

3: Geometrical principles of tomography: The fundamental idea of photographing sections of the body, as introduced by Bocage, is to coördinate the motion of the tube and the film around an object which remains fixed during the exposure. Objects on the particular plane which is in focus are thus constantly projected on the same point of the film, while objects lying in any other plane (not in focus) throw their shadows on different points of the film; as a result of this continuous movement or "wandering," effacement of the shadows is produced. The greater the distance of these points from the cross-section in focus, the greater is the degree of their erasure.

Figure 2 shows how this takes place. T_1 and T_2 represent the initial and final positions of the tube during the exposure. In the initial position T_1, the image of the object, a–b, is projected to a_1–b_1 on the film; in the final position T_2, the image is projected to a_2–b_2; but in the time

that the tube has moved from T_1 to T_2, the film has moved from position 1 to position 2, and thus the image of a–b falls on the *same* two points of the film. On the other hand, the point P, lying in a plane which is not in focus, is projected to *different* points on the film during the synchronized movement of the plate and the tube, and thus at no time is it exposed for a sufficiently long period to produce an image.

Starting from the geometrical proof of this idea, Bocage believed that the longer and the more complete he could make the excursion of the tube,

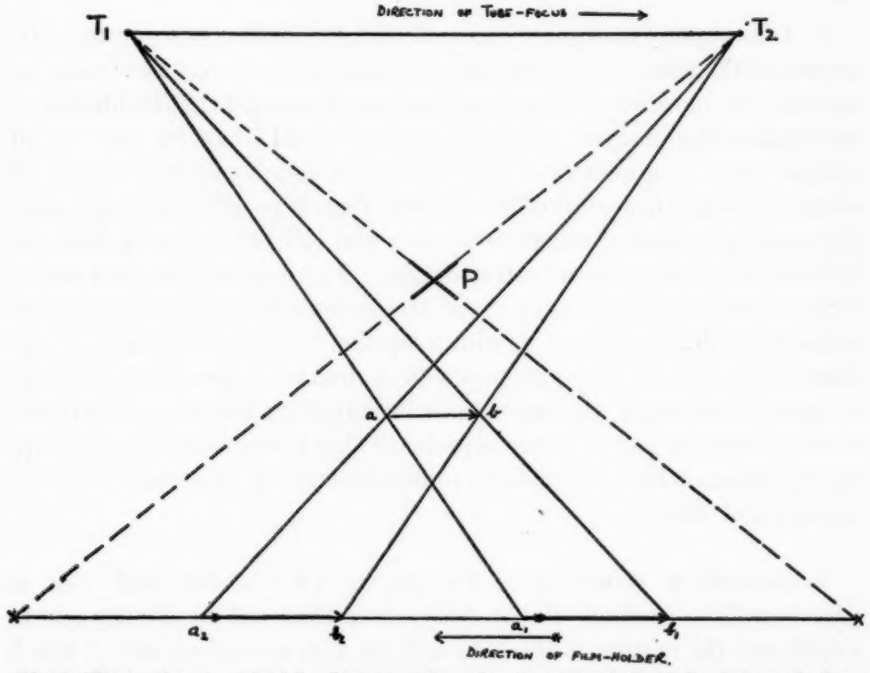


Fig. 2. Illustrating the principle of tomography: showing "wandering" of points not in focus

the more effective would be the effacement of shadows of objects above and below the particular section to be reproduced. In this he was followed by later workers in this field, particularly Bartelink and Vallebona, who, as a result of a mistaken geometrical approach to the problem, suggested that the tube should move along an Archimedean spiral (Bocage), a sinus line (Bartelink), or some other type of curve which as nearly as possible would produce effacement of unwanted shadows. But such a motion, that is, around one axis, is only adequate for the representation of small fields; for the photography of a large area, movement around two axes becomes necessary.

With such methods of moving the tube the apparatus becomes increasingly complicated, and long exposures were found to be necessary. Furthermore, difficulties arose with the Potter-Bucky diaphragm as a result of which the film became partially shaded by the grid elements of the diaphragm. The loss of time in exposure caused by these diaphragm shadows could only be avoided by imparting a complicated motion to the diaphragm, similar to that described by the tube, and the final result was that the apparatus they elaborated was hardly practicable for routine X-ray work and consequently failed to be adopted.

3. DESCRIPTION OF PRESENT APPARATUS

In the modern tomograph apparatus, constructed in 1935 to the plans of Grossman and Chaoul of the X-ray department of the Charité University Clinic of Berlin, the motion of the tube has been considerably simplified and the use of a diaphragm made possible.

Figure 3 is a photograph of the apparatus, showing the tube in the initial position of the pendulum. The machine, as manufactured by the Sanitas Electrical Company of Berlin, and as used by us, consists essentially of a two-armed pendulum oscillating about a horizontal axis. To the upper and longer arm, which is above the table, is attached a supporting lever for the tube. To the lower and shorter arm, below the table, is attached a rectangular holder which contains the Potter-Bucky diaphragm and the film-holder. The tube-container may be moved both vertically and horizontally. The difficulties with the diaphragm in the early types of apparatus noted in the preceding section are avoided by moving the tube in a plane perpendicular to the layer to be radiographed. This is achieved by arranging that the plane of the middle-grid element coincides with the plane in which the focus is moved. The pendulum itself is fixed to a block, which is suspended between a stand of two posts in such a way that the block can be moved up and down and fixed in any desired position. Above the tube, and attached to it, is a pulley system running on an arc. The fixation block contains a graduated scale by means of which the extent of the swing of the tube is controlled. The pendulum is pulled over to the initial position at one end of the arc by releasing a pin in the centre of the block.

4. TECHNIQUE OF EXAMINATION

1: Procedure: Tomographic investigation should only be used after having completed the routine radiological examination of the patient by

means of screening and the usual X-ray photograph. The depth of the patient's chest is measured in full inspiration, and the calculations are

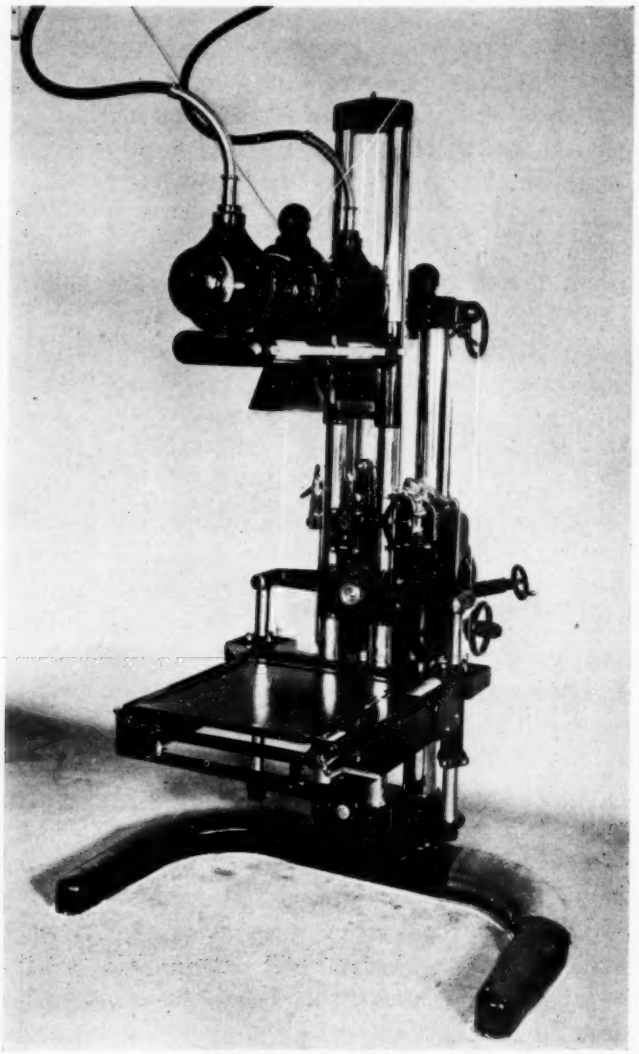


Fig. 3. The tomograph

made for the sections of the chest required. It is at once apparent that the number of sections which may be reproduced is limited only by the depth of the patient's chest; but the question had to be settled, not least

from the point of view of economy and the time at one's disposal, as to the number of tomograms to be taken in each case to provide adequate diagnostic information. Following the practice of Chaoul, we take three photographs, as follows, as a routine in each case:

1: Ventral, that is, about 7 cm. from the front of the chest-wall.
2: Median, that is, about midway between the front and the back; this usually corresponds approximately to the level of the hilum of the lung.
3: Dorsal, that is, about 7 cm. from the back.

Should the distribution of the lesion be such that it is advisable to take further sections, it is our practice to take premedian, predorsal and postdorsal photographs at depths of 2 cm. in front of or behind the corresponding main sections enumerated above. It is only rarely, however, that as many sections as this have to be taken to establish the site and distribution of the lesion.

The distances required for the three standard sections having been obtained, the tube is adjusted to the required height and then swung over to the initial position at one end of the arc. The cassette is placed in position on the film-holder, the diaphragm is set, and the machine is then ready to take the required photograph.

2: Position of the patient: The position of the patient varies according to the photograph to be taken. For an ordinary frontal cross-section of the chest, the tube should move in a direction parallel to the body axis; thus the patient lies in the long axis of the table. In the case of lateral sections, the direction of the tube must be transverse to the body; this is achieved by having the patient lying across the table. The importance of this lies in the fact, first pointed out by Grossman, that the tomograph gives blurring in one direction, and, to overcome this, it is necessary to move the tube in a direction perpendicular to the direction of the shadows. This requirement is satisfied by adjusting the position of the patient in the manner described above.

3: Exposure and technical considerations: The time of exposure is usually one second for taking section photographs. This may appear to be a long period, but experience has shown that it is with this time of exposure that the best results are obtained. The voltage and strength of the current are varied for the different sections to be taken. For ordinary frontal sections, a 6-kilowatt tube is ample, but for lateral sec-

tions a 10-kw. tube is necessary. The optimum voltage and current for the frontal sections is 60–65 kv. with 70–150 ma., working at a distance 0.90 to 1.50 metres between the section and the film. For lateral photographs, voltages between 80–90 kv. are used with a current of 150 ma., the time of exposure being the same.

Voltage and strength of current may be altered in different cases according to the thickness of the patient and the density of the lesions.

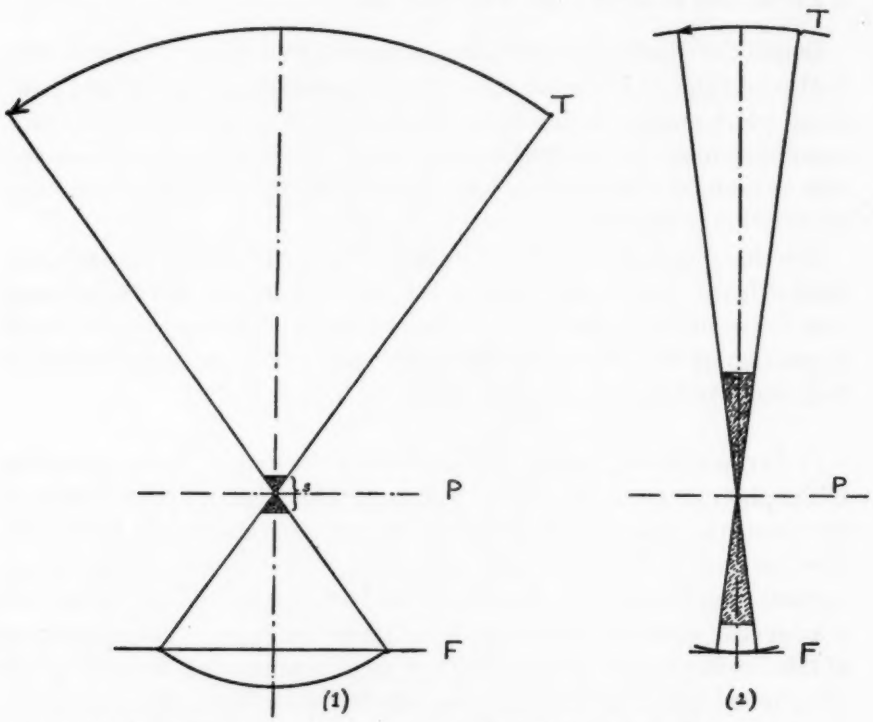


Fig. 4. To show relationship between width of section and angle of elongation

4: Width of section: In the apparatus of Bocage, the stratum of the body which was photographed was extremely thin and was really of little value from the point of view of diagnosis. Chaoul has modified this in the apparatus described above, and, as a result, a stratum of any desired thickness may be reproduced. Actually, the thickness of the cross-section varies with the extent of the arc described by the tube,—the greater the arc the thinner is the layer, and the smaller the arc the thicker is the layer,—so that when the arc is at its minimum (that is, nil), and

the tube does not swing at all but remains at rest, the section which is then reproduced comprises the entire thickness of the chest and is really not a "section" at all. That is to say, the tomograph apparatus is then being used as an ordinary radiographic machine and thus takes the usual X-ray photograph of the chest.

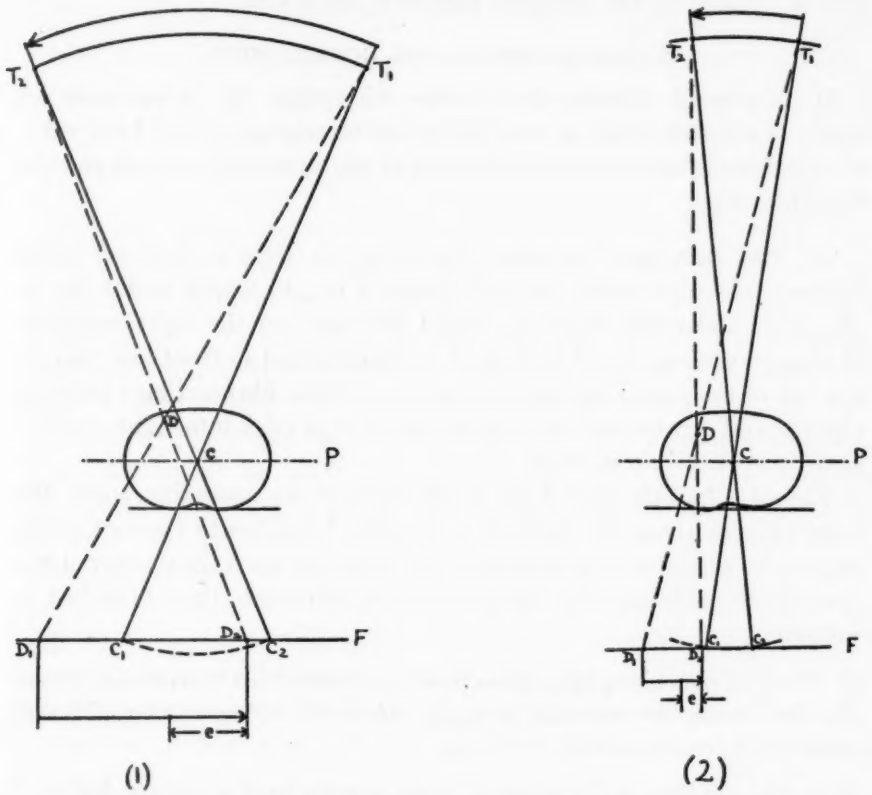


Fig. 5. To show relationship between degree of erasure and angle of elongation

Figure 4 is a geometrical representation of the proof that the thickness of the section depends upon the angle of the arc described by the tube. The plane P represents the section in focus; T is the path of the tube, and F the position of the film, with S as the thickness of the section. The variation in S is clearly brought out in positions 1 and 2. The degree of effacement of unwanted shadows, and consequently the clarity of definition of the picture, is also dependent upon the angle of elongation, as is shown in figure 5.

Position 1 shows the projection of a point D which is above the section in focus; to determine the degree of effacement of this point, the distance C_1–C_2 (representing the projection of an object in the centre of the plane, on to the centre of the film) is subtracted from the distance D_1–D_2, and is given by E in the diagram. In position 2, where the angle of elongation is diminished, the degree of erasure is much less.

5. TOMOGRAPHY OF THE NORMAL LUNG

1: Anatomical introduction: Before discussing the appearance of layers of a normal lung, as revealed by the tomograph, it will be of value to describe the anatomical distribution of the pulmonary vessels and the bronchial tree:

(a) *The pulmonary arteries:* According to Gray's *Anatomy* (23rd edition), the pulmonary artery is about 5 cm. in length and 3 cm. in diameter, and arises from the conus arteriosus of the right ventricle. It then runs upward and backward, passing at first in front and then to the left of the ascending aorta to the level of the fibrocartilage between the 5th and 6th thoracic vertebrae, where it divides into right and left branches of nearly equal size.

The *right* branch runs horizontally behind the ascending aorta and superior vena cava, but in front of the right bronchus to the root of the right lung, where, according to W. Felix, it lies between the eparterial and the hyparterial bronchi; it then proceeds to divide into three branches, as follows:

(i) Two branches to the upper lobe, running in front of the eparterial bronchus.
(ii) One branch, the main one, to supply the middle and lower lobes; this runs underneath the hyparterial bronchus.

Even the further ramifications of these vessels have a certain degree of regularity, despite individual variations, and it is possible to identify the following peripheral distribution in the right lung:

(i) In the upper lobe, three vessels, namely, ventral, apical and dorsal branches.
(ii) In the middle lobe, three vessels, namely, one dorsal and two ventral.
(iii) In the lower lobe, three superficial branches (ventral, median and dorsal), and one deep branch descending along the mediastinum.

The *left* pulmonary artery runs horizontally in front of the descending aorta and the left main bronchus to the root of the left lung, where it divides into two main branches for each lobe of the lung. Here again,

the larger vessel is the branch to the lower lobe. The peripheral distribution to the lobes of the left lung is as follows (after Greineder):

(i) In the upper lobe, five branches may be traced, namely, dorsal, apical and ventral branches, and two branches to the lingula.
(ii) In the lower lobe, three superficial branches, namely, dorsal, apical and ventral, and one deep branch descending along the mediastinum.

The description given above, in which each lobe has a principal vessel dividing into several branches, is true for the great majority of cases, but a so-called aberrant type has been described in which the lobes are supplied by several branches entering them at different points.

(b) *The pulmonary veins:* These are four in number, two from each lung, and are formed by the joining together of venules coming from the capillary network on the walls of the alveoli of the lungs. One vessel is formed from each lobule of the lung, and these vessels, uniting successively, form a single trunk from each lobe, three from the right lung and two from the left; the vein from the middle lobe of the right lung generally unites with that from the upper lobe, so that ultimately two veins, a superior and an inferior, leave each lung, but occasionally the three veins on the right side remain separate. At the root of the lung, the superior pulmonary vein lies ventrally, in front of, and a little below, the pulmonary artery and the main bronchus; the inferior is situated at the lowest part of the hilum and on a plane posterior to that of the superior vein. It is only in the internal portion of the lungs that the veins accompany the arteries and bronchi; toward the surface of the lungs the veins pursue a separate course and run in the connective tissue septa between the small lobuli, while the arteries ramify in the actual centre of the lobule.

(c) *The bronchi:* The bifurcation of the trachea into the two bronchi occurs at the level of the upper border of the 5th thoracic vertebra.

The *right* bronchus is wider, shorter and more vertical than the left, and is about 2.5 cm. long, entering the right lung nearly opposite the 5th thoracic vertebra. The azygos vein arches over it from behind, while the right pulmonary artery lies at first below and then in front of it. The peculiarity of the right bronchus is that it gives off an eparterial branch, so called because it arises above the right pulmonary artery; it supplies the upper lobe of the right lung. The continuation of the

main bronchus is known as the hyparterial branch: this passes below the artery and divides into two branches for the middle and lower lobes of the lung respectively.

The *left* bronchus is narrower but longer than the right, being nearly 5 cm. long, and enters the hilum of the left lung opposite the 6th thoracic vertebra, passing beneath the arch of the aorta. The left pulmonary artery lies at first above and then in front of it; there is no eparterial branch to the left bronchus.

2: Description of a tomogram of a normal lung: Figure 6 is a tomogram of the lung of a normal healthy adult, taken through the level of the hilum, that is, a median section. The first feature which will be noted

Fig. 6. Tomograph of normal lung

is the absence of the rib-shadows over the lung area; it is only at the lateral margin of the thorax that small parts of the ribs are visible where they have been cut by the section.

The lung field appears as a uniform background traversed by the radiating pulmonary structures coming from the lung root. It will be observed that the tomogram, in comparison with the usual type of skiagram of the chest, gives a slight loss in definition, but this is not of such a degree as to detract from its value in diagnosis. The cardiac shadow shows no material difference from that seen on an ordinary X-ray, except that its transverse diameter is clearly greater on the ventral photograph than on the dorsal by reason of its anatomical situation. The trachea, however, shows up with considerable clarity as a transparent strip running down to its bifurcation, and the bronchial divisions

may be traced to their peripheral ramifications; the main bronchi, in contrast to the pulmonary vessels, show up as transparent structures.

On the right side, the eparterial and hyparterial divisions of the bronchi may be identified, with the shadow of the pulmonary artery between, and the continuation of this vessel to the lower lobe can be followed. Accompanying this branch is the bronchus to the lower lobe, and on the medial side of this, between it and the cardiac margin, is the shadow of the vein running to the lower lobe. In a dorsal-section photograph, the deep descending branch of the pulmonary artery may be identified close to the mediastinum. In the upper lobe, the various branches of the artery may be clearly seen: two running in a vertical direction to the apex, and one more or less transversely.

On the left side again, the distribution of the vessels may be followed without difficulty. In this film, an interesting feature is the presence of a small calcified lymph node in the right upper zone, with a second one at the hilum.

Greineder has published a series of lateral tomograms of the normal lung which are of particular value in showing the relations of the structures at the hilum. Considerable care is required, however, in the interpretation of these pictures; but certainly structures which normally are never, or at best only indistinctly, seen are revealed with astonishing clarity.

6. TOMOGRAPHY IN PULMONARY LESIONS

1: The analysis of gross disease: In discussing the value and significance of tomography in pulmonary cases, we shall begin with two cases in which the ordinary dorsoventral skiagram revealed a gross lesion which normally would have been considered to portray a certain pathological process, but which, in fact, entirely failed to give an accurate representation of the exact nature and distribution of the lesion. The ordinary skiagram was not lacking in technical efficiency, but, because it can only show a summation of all the shadows coming within the area of the rays, it necessarily failed to give an exact conception of the disease. It is true that those physicians and radiologists who regularly adhere to Osler's dictum, and follow up their cases to the postmortem table, are soon made aware of the considerable degree of disease that remains unrevealed by the X-ray machine, but it is only too common to find the belief that the X-ray picture is infallible, and the final arbiter of the patient's destiny. And if tomography will serve only to demonstrate the wealth of

disease which may lie unsuspected, and thus to provide a useful corrective to our former opinions, it will have served its purpose.

Case 1: Figures 7a, b, c and d give a series of films of a patient, S. A. B., admitted to Preston Hall Sanatorium.

Figure 7a is the usual dorsoventral skiagram taken on admission. The *right* lung shows an extensive diffuse lesion involving the upper and mid zones, and appears to be of a highly active type; there is, however, no definite indication of cavity-formation. The *left* lung reveals a large cavity in the upper lobe, with two stout fibrous bands traversing the lower portion of the cavity; over the remainder of the lung there is extensive infiltration with the characteristic "fluffy" appearance of exudative disease.

Figure 7b is a ventral tomogram of the same case, taken 7 cm. from the front of the chest. It will be observed how clearly the trachea is revealed, even the larynx standing out with extreme clarity, and both the thyroid cartilage and the cricoid cartilage are easily identified, together with the narrowing produced by the vocal cords. On the original plate (though not, perhaps, on the reproduction shown here) the actual serrations produced on the internal surface of the trachea by the tracheal cartilages may be made out without difficulty. Taking the lung fields, we find the lesion on the *right* side to consist, at this level, of discrete, scattered nodules over all zones, but most dense at the apex. Otherwise, there is nothing definite to be noted in this lung. On the *left* side, the cavity is seen to be occupying almost the whole of the upper lobe ascending to the very apex, but the fibrous bands of the first film do not appear; the lower lobe is now seen to contain a large, irregular cavity at the base and adherent to the diaphragm, and above this are several smaller cavities, none of which were apparent on the first film.

Figure 7c is a reproduction of the median tomogram, taken midway between the front and the back of the chest. The trachea is now seen to be pulled over to the left side, and, lower down, the division into the two bronchi may be seen, the hyparterial bronchus on the right showing up particularly well, together with its continuation into the substance of the lung. The *right* lung now shows the genesis of a cavity-system in the upper lobe, with several scattered acinous nodules in the mid zone; the pulmonary artery is seen as an opaque mass between the eparterial and hyparterial bronchi. On the *left* side, the origin of the fibrous bands may just be seen at the base of the cavity, which remains very large and

without any definite lateral wall,—almost suggestive of a localized pneumothorax; in the lower lobe, the cavities noted on the ventral film have now disappeared, their place being taken by diffuse disease, which again is almost suggestive of consolidation of this portion of lung.

Figure 7d is the dorsal tomogram, taken 7 cm. from the back of the chest. The posterior portions of the ribs are now coming into view, the

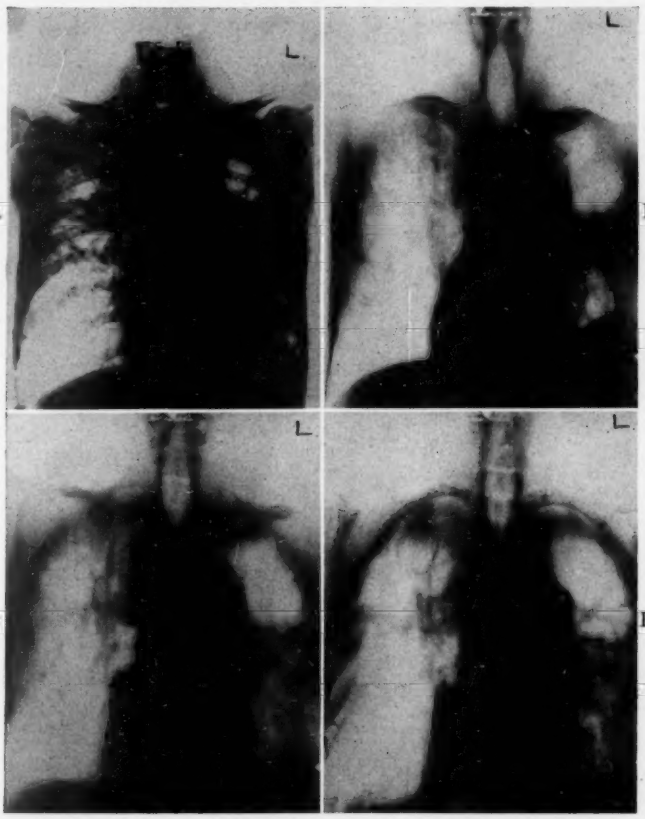


Fig. 7a Fig. 7b

Fig. 7c Fig. 7d

Figs. 7a, b, c & d. Case 1. For description see text

shadow cast by the first rib being particularly prominent; also, the cardiac shadow is now much narrower. The *right* lung is now seen to contain two large thick-walled cavities in the upper lobe, with dense infiltration in the mid zone; the lower lobe, however, remains comparatively clear. The *left* lung is now shown to have one large cavity in the upper lobe, with the fibrous bands producing a loculated appearance

below; the lower lobe remains densely infiltrated, and the actual extent of this, well behind the heart, can be made out.

Thus, in this case, we are enabled to construct, section by section, the actual lesion with its distribution through the chest.[3]

Case 2: Figures 8a, b, c, d, e, f and g are reproductions of the tomograms in the case of F. P., a patient admitted for treatment at Preston Hall Sanatorium. Whereas in the preceding case the standard four films, that is, dorsoventral, ventral, median, and dorsal, were taken as the basis of the discussion, in this case we have taken a larger series because of the many interesting features revealed by the standard group which were taken in the first instance, and also to illustrate the method and potentialities of successive sections.

Figure 8a is the usual skiagram of the chest; reading this film, one can say that the *right* lung contains old-standing fibrotic disease of the upper lobe with two cavities below the clavicle: one close to the mediastinum and the other toward the lateral margin of the lung; in addition, the outer cavity appears to have a knuckle of fibrous tissue within its lumen. In the mid zone, there is an area of recent infiltration which appears active, and the right leaf of the diaphragm is peaked and adherent, with obliteration of the costophrenic angle. The *left* lung shows infiltration of a "hard" type over the upper and mid zones, with two cavities in the 4th intercostal space; the lower lobe appears free from disease but somewhat emphysematous, and the left leaf of the diaphragm is sharply outlined.

Figure 8b is that of the ventral tomogram taken at the usual 7 cm. from the front. The *right* lung shows a scattered area of patchy consolidation (calcification ?) over the upper and mid zones; in the lower lobe there is a small, well-defined cavity, but no cavities are visible in the upper lobe. The right leaf of the diaphragm shows one adhesion, but is otherwise well outlined. Over the *left* lung, there is infiltration of an indefinite type involving the upper and mid zones, but nothing more. The trachea shows up clearly, and is seen to be central in position without any deviation.

Figure 8c shows the premedian section, at a depth of 9 cm. from the front, that is, a further 2 cm. behind the preceding section. There is no striking change to be noted on the *right* side, both the scattered consolidation and the lower-lobe cavity showing up more clearly. But

[3] Postmortem verification of these findings has since been obtained in this case.

Fig. 8a

Fig. 8b

Fig. 8c

Fig. 8d

Fig. 8e

Fig. 8f

Fig. 8g

Figs. 8a, b, c, d, e, f & g. Case 2. For description see text

on the *left* side, the vague infiltration is now being replaced by definite shadows suggestive of cavitation in the upper and mid zones. An interesting feature is the presence of a triangular area of fibrous tissue at the level of the hilum of the lung.

Turning to the next section shown in figure 8d, which is midway between the front and the back of the chest (11 cm. from the front and a further 2 cm. deep to the previous section), the first point to be noted is the clarity with which the trachea is revealed. The actual bifurcation, with the right and left bronchi and their subdivisions, may be easily traced. The *right* lung, in this section, shows considerable differences from the previous photographs; the thickening of the upper interlobar septum is now visible, with prolongations of fibrous tissue to the periphery, and, in addition, an air space is now present in the upper lobe which is suggestive of cavitation; in the lower lobe the small cavity previously noted has now disappeared, and its place is taken by an area of diffuse infiltration. In the *left* lung the cavities in the upper lobe are now better defined, and the sharp knuckle of fibrous tissue above the pulmonary artery is very prominent.

Figure 8e is a tomogram of the predorsal section, taken a further 2 cm. deep to the preceding level, and now only 9 cm. from the back of the chest. The trachea and portions of the bronchi are still clearly seen, while over the *right* lung the air space in the upper lobe is increasingly well defined; in addition, a cavity is coming into view close to the mediastinum, but the infiltration in the lower lobe is fading. In the *left* lung, a cavity which was previously not visible is now coming into view in the lower mid zone.

Continuing a further 2 cm. into the chest, we have the dorsal section, shown on figure 8f, which is 7 cm. from the back. On the *right* side, two air loculi are now apparent over the upper and middle lobes, divided by a band of fibrous tissue about the level of the interlobar septum. The appearances are strongly suggestive of a localized spontaneous pneumothorax. Close to the mediastinum, in the inner part of the upper lobe, there is now a well-defined cavity, whilst over the lower lobe diffuse infiltration is now visible with the multiple adhesions to the diaphragm which were visible on the dorsoventral picture (figure 8a). On the *left* side the cavities in the upper lobe are fading, their place being taken by fibrous tissue; the cavity in the mid zone is now very well defined.

The final picture, taken as a postdorsal section, 5 cm. from the skin of the back of the chest, is shown on figure 8g. The air-space in the *right*

lung, previously noted, is now even more sharply defined; otherwise, the lung appears as on the previous section, except that the infiltration over the lower lobe has now broken down in parts, with the resultant formation of a cavity system. The *left* lung shows no material difference, except that the mid zone cavity stands out very sharply.

It is no exaggeration to say that it is quite impossible to deduce the actual pathological nature of the lesion from a study of the ordinary film, and the existence of the spontaneous pneumothorax must have remained unsuspected. The manner in which one series of cavities comes into view as another group begins to fade illustrates in the clearest manner the topography of the lesion. In broad outline, the series also shows how the main lesion is situated in the deeper portions of the lung tissue. This finding is borne out by our remaining cases. Pulmonary tuberculous lesions usually predominate at the back of the lungs, and extend by advancing forward into the anterior sections. Hence it may often occur that the ventral tomograms are quite free from disease, while the dorsal sections may show old-standing chronic disease.

2: The diagnosis of cavities: Case 3: This case is described as an example of the value of the tomograph in revealing cavities, the existence of which may not be even suspected. The previous cases have illustrated the value of tomography in *dissecting*, as it were, a gross lesion. It might be argued that the two cases already described revealed disease in which the presence of cavities might at least have been inferred on the ordinary film, without actually identifying their walls; in particular might this be said of case 1. But in the following example, we feel that no amount of hypothetical conjecture could have exposed the areas of cavitation which were revealed by the tomograph.

Figure 9a is the X-ray picture of the chest in the case of D. Q. There is well-marked fibrosis of the upper and mid zones of both lungs, and below the left clavicle is a chronic cavity; no other areas of cavitation are revealed. Figures 9b, c and d are reproductions of the ventral, median and dorsal tomograms respectively. In the ventral section an area of disease in the *left* mid zone may be seen, with a shadow suggestive of breaking-down lung tissue; on the *right* side one or two calcified lymph nodes are visible, but there is no infiltration as yet. The median section shows a startling difference; apart from the clarity with which the eparterial and hyparterial divisions are revealed, there has now come into

Fig. 9a

Fig. 9b

Fig. 9c

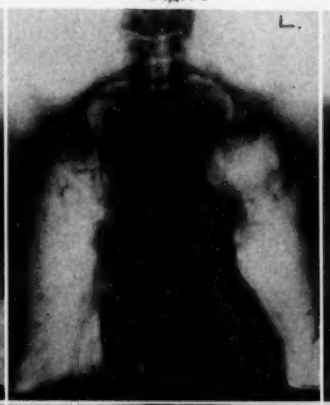


Fig. 9d

Fig. 10a

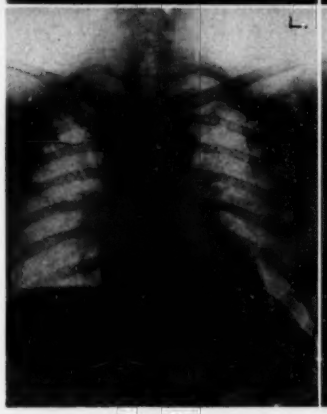


Fig. 10b

Fig. 10c

Fig. 10d

Figs. 9a, b, c & d. Case 3. For description see text
Figs. 10a, b, c & d. Case 4. For description see text

view a thick-walled cavity in the apical portion of the *right* middle lobe, with an area of fairly dense infiltration in the upper lobe. On the *left* side, the previously noted shadow in the mid zone is now clearly a cavity, and, in addition, there are now shadows over the upper zone which suggest cavitation. This is confirmed in the dorsal tomogram, where the left upper lobe cavity is sharply defined.

Thus the actual lesion consists of (1) multiple cavities in the upper lobe of the left lung, situated medially and dorsally; and (2) cavitation in the middle lobe of the right lung at about the depth of the hilum.

3: The localization of cavities: Two cases will now be described illustrating the precise localization of a cavity which was visible on the ordinary anteroposterior film of the chest.

Case 4: Figures 10a, b, c and d are reproductions of a series of films in the case of F. A. L.; the first of these shows a large, thick-walled cavity below the clavicle on the *right* side. But the tomogram of the ventral section reveals the lung to be, as yet, quite free from disease; the median section also fails to reveal any infiltration. The dorsal section, however, shows the large cavity to be present and also confirms the absence of disease in the other lung.

Following this finding, a successful apicolysis with posterior *plombierung* was performed.

Case 5: The next case is described because of the interesting loculation of the cavity which is revealed by the tomograph, in addition to the exact localization of its site. Figure 11a is that of the ordinary skiagram of the chest; a large, chronic, thick-walled cavity is present in the *right* upper lobe, with considerable thickening of the interlobar septum below; there is also some chronic fibrosis of the *left* apex. The ventral section, shown on figure 11b, reveals the thickening of the septum to be already present, with shadows of two cavities in the *right* upper lobe coming into view; note also a bronchus near the hilum sharply defined in cross-section.

The median section (figure 11c) reveals a "double cavity" system with a stout fibrous band between; furthermore, the two divisions of the eparterial bronchus can just be seen to enter the outer wall of the joint cavity system.[4]

[4] The reproduction of the films can never hope to reveal the various points with that accuracy and clarity of detail which is seen on the original tomograms.

Fig. 11a

Fig. 11b

Fig. 11c

Fig. 11d

Fig. 11e

Figs. 11a, b, c, d & e. Case 5. For description see text

The dorsal section (figure 11d) illustrates how these two cavities in the right upper lobe have now fused, with the resultant formation of a very large, single cavity; a peculiar thickening of the inferior margin of this cavity may also be noted. We have observed a similar occurrence on a number of occasions, sometimes associated with an actual protuberance into the lumen of the cavity; while these probably represent an area of proliferation of fibrous tissue, we would not like to be dogmatic as to their exact pathological interpretation, and mention them simply as having been observed.

By the time we reach the postdorsal section, shown on figure 11e, the large cavity has, however, almost completely faded, thus establishing that the main distribution of the lesion in this case is really medially and slightly posteriorly.

4: Tomography in cases following thoracoplasty: There is little need for us at this stage to stress the difficulties in ordinary radiological examination of cases following extensive thoracic operations, such as a complete paravertebral thoracoplasty. In order to penetrate the dense fibrosis which occurs after the operation, a degree of penetration has to be used which leads to a "blackening" effect of the contralateral side, and the basis of comparison with the nonoperated side is seriously interfered with. Some have suggested the use of lead plates to be held over the normal lung, while the operated side is subjected to an extra exposure in order to penetrate the dense structures.

Tomography surmounts this difficulty and is therefore of especial value in such cases; indeed, it is in the investigation of this type of case that tomography has been widely used in the clinic of Professor Sauerbruch in Berlin; and the next case to be described in this series will be that of a patient who had undergone a thoracoplasty but still had a positive sputum some time after the operation.

Case 6: The patient, R. S., had been sent to Preston Hall for investigation. Figure 12a is a reproduction of the dorsoventral film of his chest; a paravertebral thoracoplasty has been performed of the upper 7 ribs, with an excellent resultant collapse of the right upper lobe; no cavity or definite area of disease is present which might account for the persistence of the positive sputum.

The ventral film revealed nothing of note, and is not reproduced here, but the median, predorsal and dorsal sections, shown in figures 12b,

c and d, respectively, indicate, first, the genesis of an area of infiltration in the right lower lobe below the operated area; then a more definite shadow strongly suggestive of early cavity-formation; and, finally, the gradual disappearance of this shadow. That this was the area of disease giving rise to the positive sputum was further supported by the physical signs over this portion of the chest, and the two, taken together, left little doubt that this was the further focus of infection.

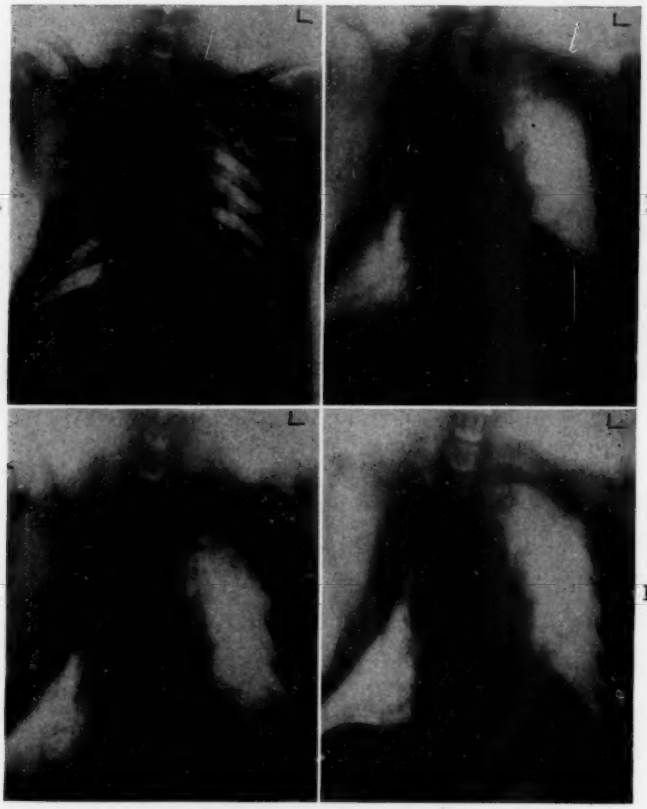


Fig. 12a

Fig. 12b

Fig. 12c

Fig. 12d

Figs. 12a, b, c, & d. Case 6. For description see text

5: On the zone of collapse in artificial pneumothorax: Cases of artificial pneumothorax provide some of the most interesting material for tomographic investigation. Not only can the extent of the pneumothorax be easily demonstrated, but also the site and the nature of adhesions; and the case to be described is typical of many which we have examined by this means.

Fig. 13a

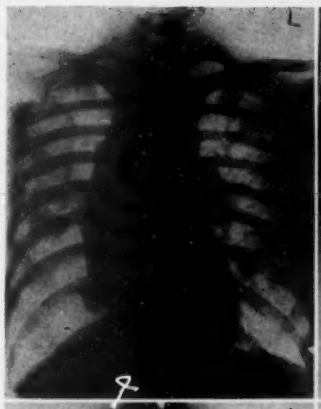
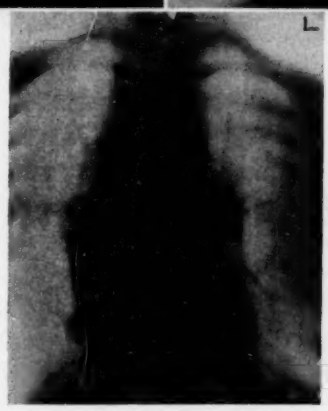


Fig. 13b

Fig. 13c

Fig. 13d

Fig. 13e



Figs. 13a, b, c, d & e. Case 7. For description see text

Case 7: Figures 13a, b, c, d and e represent a series of films in the case of L. S., who was admitted for treatment with an extensive lesion of the right lung, and involvement of the left mid zone. An artificial pneumothorax was induced on the right side following haemoptysis; a good collapse was obtained, which was prevented from being complete by the presence of two adhesions over the upper and mid zones. An effusion developed later which was treated by aspiration and air-replacement; figure 13a is a dorsoventral film, taken after the completion of such a procedure, and the degree of collapse on the right side is well illustrated. In addition, a collection of fibrinous material, which is almost polypoid in type, may be seen at the base of the collapsed lung; the left lung shows a fairly diffuse infiltration of the mid zone.

Turning to the tomograms of the case, we find that in the ventral section (figure 13b) the degree of collapse is very good, neither adhesions nor collection of fibrin showing. The median section, figure 13c, (which incidentally reveals the left bronchus particularly well) still fails to show the presence of adhesions, but the faint shadow cast by the fibrinous collection may just be detected. Two centimetres deep to this, in the predorsal section (figure 13d), both the upper-lobe and mid-zone adhesions are clearly exposed, together with two partially compressed cavities in the middle and lower lobes; the mass of fibrin is also clearly seen. In the dorsal section (figure 13e), which is a further 2 cm. behind the preceding level, there is a greater degree of collapse, but the adhesions are still faintly visible. Thus the lung is, as it were, billowed posteriorly, coming out to a certain extent in the median depths and being well collapsed again anteriorly, this effect being produced by the position of the adhesions, which are also situated medially.

A similar state of affairs has been revealed in other cases, and it would appear to be a not unusual finding in artificial pneumothorax for the collapse of the lung to be far from uniformly distributed; there may be an almost complete collapse over the anterior portion of lung, and yet the posterior zones may be unaffected, usually because of the presence of multiple small adhesions. When there are only one or two cord-like adhesions, they are more commonly found to be situated medially.

7. CONCLUSIONS

In this paper we have limited the description and discussion of results of tomographic investigation to cases of pulmonary tuberculosis, because, as yet, our experience of this adjunct to diagnosis in other conditions is

hardly wide enough either to warrant a description of the results or to enable us to come to any decision upon its value in such conditions. We have had under investigation cases of Hodgkin's disease, intrapulmonary cysts and lung abscess; but the field of cranial tomography has not been touched by us, and in the opinion of Chaoul this will be a particularly valuable field for investigation. There are also possibilities in the direction of tomography of the heart which remain to be explored, but, clearly, many modifications in technique will have to be elaborated before this particular organ can be demonstrated in recognizable sections. Nevertheless, despite the possibilities of tomography in a variety of conditions, it is our opinion that its greatest value at the moment lies in pulmonary tuberculosis, which manifests itself in such divers ways that, even with every method at our command, the problem of diagnosis is at times very difficult.

While indicating its value, we have no desire to make exaggerated claims for tomography, and the indiscriminate use of the apparatus in all cases is certainly not called for. As we have made clear in a preceding section, tomographic investigation should only be used after routine radiological and screening examinations have been completed; it is then that problems calling for further elucidation may arise, and that tomography may be utilized as an additional aid. It is felt, however, that the cases described support the opinion that in tomography we have a valuable adjunct to the diagnosis and interpretation of pulmonary lesions, and an addition to the armamentarium of the physician and surgeon which one cannot afford to neglect.

8. SUMMARY

1. The sources of difficulty in the interpretation of a skiagram of the chest are discussed, and the need shown for some method whereby these difficulties may be overcome, either in part or in whole.

2. The method evolved—tomography—is described, and its advantages discussed.

3. The history of the development of the geometrical principles of tomography is described, and the difficulties of earlier workers in overcoming the practical problems of constructing a workable apparatus are discussed.

4. The present apparatus of Grossman and Chaoul is described, together with the technical points to be observed in the taking of tomograms.

5. A description of the tomogram of a normal lung is given, with a

résumé of the anatomy of the intrapulmonary structures, in order to establish a basis of comparison with films illustrating pathological lesions.

6. Seven cases of pulmonary tuberculosis which have undergone tomographic examination are detailed, with special reference to (1) the analysis of gross disease, (2) the diagnosis of cavities, (3) the localization of cavities, (4) value of tomography in cases following thoracoplasty, and (5) the type of collapse in artificial pneumothorax.

7. The possibilities of tomographic examination in other areas of the body, such as the skull and the heart, are mentioned, but it is clear that modifications in technique will be required before this new line of work can be fully explored. While in no way supplanting the recognized methods of radiographic examination, it is felt that tomography, with its many advantages and refinements, cannot be ignored in the investigation of a case of pulmonary disease.

We wish to express our thanks to Dr. A. Ross for his help in the investigation of these cases.

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EXPERIMENTAL TUBERCULOSIS INFECTION IN THE TADPOLE AND THE MECHANISM OF ITS SPREAD[1,2]

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In a previous communication (1) it was shown by us that tuberculosis could be successfully induced in the tadpole of the common leopard frog (*Rana pipiens*) after feeding the tadpoles a cold-blooded strain of tubercle bacillus, namely *Mycobacterium marinum*. The structure of the tubercles that developed was found not to differ in any essential point from those produced in mammals with human or bovine strains. *Mycobacterium marinum* was first isolated by Aronson (2) from an iguana which was found dead in the Philadelphia Zoological Gardens. A number of tubercles were noted in the lungs of the animal and also in the liver. When this Mycobacterium is injected intracutaneously in the guinea pig the neighboring lymph nodes become enlarged and succulent but go on to healing. Aronson also found that a small ulcer occurs at the site of inoculation. The organism is pathogenic for the chameleon and salamander and also for the frog. *Mycobacterium marinum* is acid- and alcohol-fast. Ziehl-Neelsen stained vertical sections of growing colonies made with a technique reported by us (3) reveal some non-acid-fast rods in addition. The organism grows luxuriantly at room temperature on Petroff's egg medium in from 3 to 5 days and elaborates an abundance of orange-colored pigment.

It appeared to us that the tadpole would possibly make a valuable experimental animal for the purpose of studying the mechanism of the dissemination of tubercle bacilli in various organs of the body after having been introduced *per os*, as the entire animal can be sectioned serially and all of the organs examined in the same creature at the same time. In the following sections we are reporting the results of experiments designed for this purpose.

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[2] This study is part of a group investigation being carried on in cooperation with the Medical Research Committee of the National Tuberculosis Association.

MATERIAL AND TECHNIQUE

Young tadpoles of the leopard frog (*Rana pipiens*) were kept in sterile aquarium water contained in Stender dishes. A large loopful of a 5-day-old culture of *Mycobacterium marinum* was scraped from a slant of Petroff's egg medium and suspended in the water. After feeding on the bacteria the tadpoles were removed to other Stender dishes also containing sterile aquarium water.

Three experiments were carried out. In the first, the tadpoles were very young (5 to 7 days after hatching) and were allowed to feed on the bacteria for several days. They were soon overwhelmed without showing lesions of tuberculosis although numerous acid-fast organisms were found in the intestinal submucosa, the lungs and the liver. These tadpoles were fixed in alcohol or in a mixture of alcohol-chloral hydrate-formaldehyde, which gave better fixation.

In the second experiment, five young tadpoles were fed tubercle bacilli for one day; then they were given yolk from a hard-boiled egg during the four following days. On the fifth day they were fed tubercle bacilli again. One tadpole died during the night and could not be preserved for histological study. The other four were killed as follows: No. 1, killed 10 days after first, 5 days after second feeding; no. 2, killed 12 days after first, 7 days after second feeding; no. 3 and no. 4. killed 29 days after first, 24 days after second feeding. While only two feedings of bacteria were given it is possible that the tadpoles ingested bacilli from their own faeces, for the organisms seemingly multiply in the intestinal tract as they remain there for a long time after feeding has been discontinued. Study of the sections of the four tadpoles revealed the following conditions: No. 1, tubercle bacilli were present in the liver; first stages of formation of tubercles already seen. Also larger tubercles were in submucosa of intestine. No. 2, numerous tubercles were present in the liver, a few with beginning necrosis. No. 3, early and advanced tubercles with necrotic centers were present in liver. No. 4, mostly early tubercles; a few with beginning necrosis were found in the liver. A few tubercles containing bacilli were also seen in the spleen.

A third experiment was undertaken in order to trace the early stages of the infection. Six tadpoles were fed the Mycobacterium for one day. They were transferred to sterile water through five changes to avoid carrying over bacilli. They were killed 1 day, 2 days, 4 days, 5 days, 6 days and 7 days after feeding, respectively. Heidenhain's *Susa* fluid

was used for preservation, the fixed tadpoles being transferred directly to 95 per cent alcohol with a small amount of iodine. Although bacilli were already noticed in the mucous cells of the intestine as early as the second day after feeding, no reaction of the macrophages was observed until the sixth and seventh day.

In every case the tadpoles were dropped alive in the fixing fluid without making any cut in the skin. The tails were cut off after fixation and the whole body dehydrated, embedded in paraffin and cut into frontal serial sections (7–10μ thick). The entire animal with the exception of the tail was thus included on the slides (figure 8). The sections were stained with hematoxylin-eosin for histological details, or with the Ziehl-Neelsen technique for the staining of the bacilli. The two techniques mentioned were used alternatively in the series of slides, and in this way it was possible to obtain sections of one and the same tubercle stained with the two methods used.

PASSAGE OF THE MYCOBACTERIUM THROUGH THE INTESTINAL WALL

The presence of large numbers of bacilli within the intestine does not lead to widespread lesions of the mucosa, nor do the bacilli appear in and among the epithelial cells in a way suggesting their active penetration into the mucosa. The passage of the bacilli through the intestinal barrier is a discrete process, taking place gradually and at separate points in a more or less accidental or passive manner since the Mycobacterium is a nonmotile organism. Before describing the processes involved, it will be convenient to review briefly the structure of the alimentary canal of the young tadpole.

The stomach is lined by a mucosa containing well-developed branched tubular glands. Two types of epithelium occur, namely, ciliated epithelium consisting of columnar cells and the secretory epithelium lining the glands. The latter extend from the ciliated epithelium into the loose submucosa and many come in close proximity with the muscular layer (figure 10). In the tadpole the submucosa is represented by a small amount of embryonic connective tissue, most of which lies between the gastric glands. Outside of this there is a muscularis consisting of an inner layer of circular smooth muscle fibres, and an outer, poorly defined layer containing muscle fibres of the same variety. Finally, external to the muscularis there is a serous coat represented by a thin layer of flattened cells, separated from the muscularis by a small amount of connective tissue.

The intestines of the tadpole have thin walls and are relatively much longer than in the frog. Two regions may be distinguished: the small and large intestine, respectively, which differ chiefly in the details of their epithelial cells and the relative abundance of the two cell-types occurring in the mucosa. The latter is not thrown into conspicuous folds, nor has it villi (figures 8 and 10). It consists of columnar cells and basal round cells, the latter being relatively few in number. The columnar cells are of two types: the numerous absorptive or chief cells which are ciliated, and the less numerous mucous or goblet cells. The nuclei of both types are elliptical. In Ziehl-Neelsen preparations the cilia of the chief cells stain light pink, and the cytoplasm may take a light lavender tone, while the mucous or goblet cells stain blue (figure 1). In the goblet cells two different aspects are noticed: in some cases they appear swollen since they are distended with mucous granules, while in others they appear much more slender as a result of the discharge of the mucus. Between the two conditions there are numerous intermediate stages.

Under the epithelium of the intestine there is a submucosa, the thickness of which varies according to the region, being thinnest in the large intestine. It contains connective tissue cells of a mesenchymatous type and numerous blood-vessels and lymphatics. Tissue phagocytes (macrophages or histiocytes) containing variable amounts of pigment granules occur scattered in this layer, but in the early part of the tadpole's life they are not numerous. Outside of the submucosa there are, as in the

PLATE 1

Figures 1, 2, 5, 6 and 7 were drawn with a Zeiss apochromatic oil immersion 2 mm. (numerical aperture 1.30) and compensating ocular 15, at a magnification of 1350 diameters. Figures 3 and 4, with the same objective and ocular 20 (× 1800). Ziehl-Neelsen technique.

Fig. 1. Chief (ciliated) cell of the intestine (centre) and two empty mucous cells showing intracellular bacilli.

Fig. 2. Phagocytosis of a degenerating mucous cell containing bacilli by a macrophage.

Fig. 3. Degenerating cells containing bacilli in the intestinal submucosa. A young macrophage seen.

Fig. 4. Four different stages of degeneration of macrophages with ingested bacilli from the periphery of a tubercle of the liver.

Fig. 5. Beginning of the formation of a tubercle in the submucosa of the small intestine. Young macrophages resembling lymphocytes and containing bacilli are seen in the figure. The cell elements with pink cytoplasm at the left of the figure are smooth muscle fibres.

Fig. 6. Diverse stages of degeneration of macrophages within the lung wall of a young tadpole still breathing through the gills.

Fig. 7. Free bacilli and nuclei of phagocytes in the lumen of one of the lungs of the same tadpole represented in figure 6.

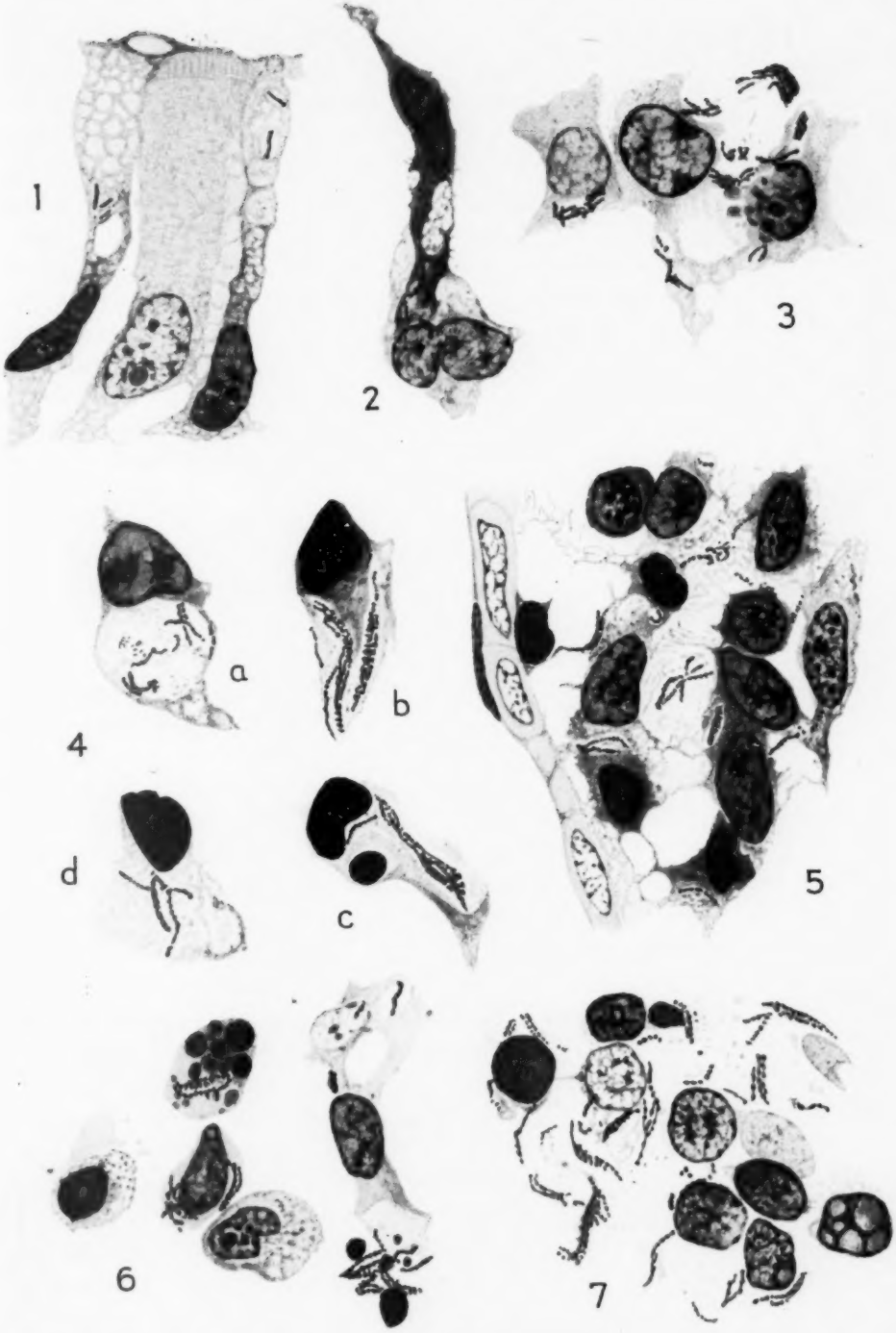

PLATE 1

stomach, two muscle coats, an inner circular and an outer longitudinal, the latter being covered externally by a thin serosa made up of much flattened mesothelial cells, closely applied against the muscle fibres in view of the very thin subserous layer.

In the large intestine the epithelial cells of the mucosa are not so tall as in the small intestine; the mucous cells are much more abundant than in the latter. The cilia of the chief cells are quite long and apparently nonmotile, being cemented together by a substance produced through secretion or transformation of the cell membrane. No glands of any kind occur in the tadpole intestine.

A study of the different regions of the intestine of tadpoles which had been fed Mycobacterium for various lengths of time has shown that this organism never occurs within the chief cells, but that it penetrates the empty mucous or goblet cells in variable numbers. Considering the very large numbers of bacilli in the intestinal lumen, the scarcity of cells containing them is rather surprising. The most plausible explanation of the presence of the Mycobacterium within the cytoplasm of the mucous cells is that the organism enters passively soon after the mucus has been extruded from the cell, and that the penetration may be indirectly helped by the peristaltic contractions of the intestine. In the stomach intracellular bacilli were never found, nor did they occur in the ducts of the gastric glands. The flow of gastric juice through the ducts may prevent their penetration.

The intracellular bacilli in the mucous cells (figure 1) appear within small, clear vacuoles. They are rather solid, short rods as compared with the bacilli within the macrophages and in the tubercles, which show a more beaded aspect. While the presence of large numbers of Mycobacterium multiplying in the intestine does not affect the cells of the mucosa in a visible way, the intracellular bacilli in the mucous cells exert a deleterious influence, causing degenerative changes and finally the death of the cell. At the beginning these degenerative changes are not easily distinguished from those changes undergone by a normal mucous cell after discharge of the mucus, but after some time their morbid nature cannot be doubted. The cell ceases to produce mucus and stains more deeply than the normal elements of its kind. The nucleus decreases in size, stains more deeply and shows a blurred aspect which may be followed by pyknosis. The cell as a whole shrinks, and may lose its connection with the surface of the epithelium, moving passively toward the submucosa where eventually it will fall prey to the phagocytes.

From the preceding descriptions, it is evident that the main portal of infection is the mucous or goblet cell of the intestinal epithelium in the absence of degenerative changes of the mucosa induced mechanically or in some other way. The chief cells are protected by their well-developed brush border, and since they are closely placed and their peripheral portions are apparently cemented together by terminal bars, the penetration of the bacilli in the intercellular spaces is effectively prevented under normal conditions. Since the mucous cells occur everywhere in the intestine, it follows that there is no definite site for the beginning of the infection.

The fate of the mucous cells containing the Mycobacterium seems to be the same in all cases, that is, they are phagocytized by macrophages occurring in the area, the phagocytosis taking place during different phases of their degeneration.

PHAGOCYTOSIS OF THE BACILLI BY MACROPHAGES

The origin and behavior of the tissue phagocytes or macrophages is well known through the exhaustive studies of E. R. Clark and E. L. Clark (4) on the tail of the living tadpole. According to these investigators, the amphibian macrophage is homologous with the mammalian macrophage, also known as histiocyte, clasmatocyte, polyblast and reticuloendothelial cell, to mention a few names. In the present article, the term macrophage will be used since it is descriptive of the main activity of this important cell-type without implying a definite origin.

The macrophages of the tadpole develop quite early and are not always derived from the blood-stream, since they may arise from the mesenchyme at a stage in which no leucocytes occur in the blood. They are the only wandering cells which take the neutral red stain to any noticeable degree. They also take up carmine, India ink and pigment granules, and engulf erythrocytes, all types of degenerating cells and extraneous substances injected in the tail such as cream, yolk of egg, starch, agar, gelatine, gum arabic and even diluted croton oil which produces an aseptic inflammation of the tissues of the tail (Clark and Clark (5) (6) (7)). After phagocytosis the cells under consideration usually develop pigment granules in their cytoplasm. In the living tadpole they often penetrate the lymphatics and blood capillaries, which they may leave after some time in the absence of any material to phagocytize. They also ingest cells before they have actually degenerated. "When a cell begins to die, the macrophages of the neighborhood make a 'bee-line'

for it. If a single macrophage reaches the dead cell, or its remnants, it proceeds to ingest them. Frequently two or three macrophages reach the dead cell simultaneously, whereupon a struggle occurs over it or its remains" (Clark and Clark (5) p. 115). Sometimes phagocytosis occurs before the various stages of degeneration of the cell have taken place. When no macrophages occur in the neighborhood, the cell may degenerate and break up and its remnants be taken up by macrophages arriving from other areas. After phagocytosis of a large mass of debris and dead cells the macrophages become sluggish and even temporarily sessile.

As to the origin of the macrophages in the tadpole tail in later stages of the larval life, the Clarks have demonstrated by actual experiments that they may also arise from large mononuclear leucocytes of the blood. In the words of these authors "the monocytes of the blood are identical with the clear mononuclear phagocytes of the tissue, and they are both capable of enlarging to form typical tissue macrophages. The large pigmented macrophage is, therefore, a monocyte which has emigrated from the blood vessel and has been carrying on phagocytosis" ((6) p. 179).

In the fixed tadpole, stained with hematoxylin-eosin or the Ziehl-Neelsen technique, the macrophages that have been engaged in phagocytosis appear as rather large cells with clear cytoplasm containing variable amounts of pigment granules, and a large, clear nucleus the shape of which is also variable. In the intestine they occur in the submucosa, and two or three of these cells may appear clustered together. It is not unusual to find bacilli in their cytoplasm, more or less masked by the pigment therein. As already stated, in very young tadpoles the macrophages are scarce. In the older larvae not only are they more abundant but many of them appear in the early stages of their development, during which they closely resemble the large mononuclears of the blood since they do not contain pigment and have a more deeply stained, basophilic cytoplasm. Such young macrophages may attack degenerating cells, and in areas of formation of tubercles they may show ingested bacilli (figure 5).

In the course of our investigations, we have been able to detect numerous cases of phagocytosis of mucous cells containing the Mycobacterium by the macrophages. In agreement with the observations of the Clarks on the tail of the living tadpole the macrophages may attack and engulf mucous cells before they have degenerated; one case of this sort has been represented in figure 2. The macrophage in this figure is seen engulfing

the basal portion of a mucous cell which has already lost contact with the surface of the mucosa, and, therefore, does not appear as tall as the more normal mucous cells of figure 1. In other instances, the macrophages attack mucous cells in which the disintegration of the nucleus and cytoplasm is much more advanced. Two or more macrophages may sometimes participate in the process, and if one or more of them should die they may in turn be engulfed by other macrophages of the submucosa (figure 3).

Although the Clarks have never been able to see the degeneration of the macrophage and regard this cell as the hardiest of all cell-types found in the tail of the living tadpole, in tadpoles infected with the Mycobacterium there are abundant examples of death of macrophages which have engulfed bacilli, either directly or through phagocytosis of cells containing them. Unquestionably the same deleterious effect exerted by the Mycobacterium on the mucous cells is exerted on the macrophages, and their death in large numbers contributes in no small measure to the formation of the necrotic area of the tubercles. It seems as though the macrophages, although able to digest cells and their debris, and some extraneous substances such as cream, yolk of egg, etc., are not able to kill the bacilli, at least in those cases in which the latter occur in fairly large numbers within the cell.

An example of degenerative phases of macrophages with engulfed bacilli is shown in figure 4, copied from the periphery of a fairly large liver tubercle. Cell *A* shows nuclear changes manifested in clumping of the chromatin granules and partial dissolution of the cytoplasm; in *B* the cell, containing a large number of bacilli, shows a clearly pyknotic nucleus, which in cell *C* has broken in two unequal parts. Finally, cell *D* shows dissolution of the cytoplasm with impending liberation of the bacilli. Similar stages are seen in figure 6, copied from the lung of a much younger tadpole, dead after 7 days of continuous feeding with Mycobacterium. The degeneration of the phagocytes is, therefore, a widespread and constant process, leading to the liberation of the ingested bacilli in the tissue in which the macrophage happens to be at the time.

Although macrophages may be killed by the bacilli which they have ingested, they do not always degenerate *in situ*, but they are able to move about and wander for some distance, a fact that would indicate that the degeneration of these cells is a slow process. Thus they are able to spread the infection. Since, as shown by the Clarks, the macrophages are able to cross the endothelium of the blood vessels and lymphatics

the vascular route of the infection deserved to be investigated carefully. We have, therefore, paid considerable attention to this aspect of the problem, to be considered in the following section.

MIGRATION OF THE MACROPHAGES WITH INGESTED BACILLI

In tracing the migrations of the macrophages with ingested bacilli we wish to emphasize the fact that the tadpoles were dropped alive in the fixing fluid, and that no cuts of any kind causing haemorrhage or spilling of the body fluids were ever made. In this regard our material differs from any material obtained from adult animals and humans. Furthermore, in our case it was possible to study *a whole tadpole in serial sections and investigate not only all the organs present during larval life but also the larger vessels and the cavities of the heart with the blood contained therein.* Under these conditions the only displacements of the cells and organs were those incidental to shrinkage during the process of dehydration and embedding.

After a study of hundreds of sections passing through the heart, the venae cavae, the portal system of the liver and the portal-renal system present in the tadpole we can conclude that macrophages containing ingested Mycobacterium do not occur in the blood-stream. This peculiar behavior is difficult to explain inasmuch as there is direct evidence of the passage of the macrophages into the blood capillaries (Clark and Clark). As to free bacilli and bacilli included within cell debris in the blood our observations are also negative. While in the latter stages of the tadpole life all the cell elements of the adult are present in the blood and the polymorphonuclear leucocytes can be distinguished from other leucocytes, repeated observations have failed to demonstrate the presence of intravascular leucocytes containing Mycobacterium.

In the serosa of the intestine, which, as already stated, is rich in capillaries, macrophages with ingested bacilli are occasionally seen within the vessels. It is difficult, however, to decide whether the phagocytic elements occur within a blood capillary or a lymphatic. We would hesitate to state, therefore, that macrophages containing bacilli do not penetrate the blood vessels, but we can say that they were never seen in vessels containing erythrocytes.

When we take into account that typical tubercles develop in the liver and occasionally also in the spleen, and that they are not seen in other organs—the intestine excepted—the most plausible explanation is that the macrophages containing bacilli reach these organs via the lymphatics, and that they are arrested there by the fixed reticuloendothelial elements

(Kupffer cells of the liver, splenocytes). It might be possible, however, that the migrating macrophages enter these organs directly after leaving the intestinal wall by crossing the thin muscularis and the serosa. In the case of the liver such penetration does not seem likely, for the youngest tubercles are to be found in the portal of this organ among the hepatic ducts.

LUNGS

Of particular interest is the presence of large numbers of Mycobacterium in the walls of the lungs and within the cavity of these organs. In the tadpole the lungs are simple sacs with thin walls, extending from the ventral aspect of the pharynx on either side of the midline. Since there is no diaphragm they lie in the abdominal cavity in contact with the organs enclosed therein, including the intestine. It is possible then, for macrophages leaving the intestine to work their way among the flattened cells of the serosa of the lungs—representing the visceral pleura of the mammal—and after crossing the lung tissue, fall into the lung cavity. During the early stages of life the tadpole breathes through gills; the lungs are still developing and appear as sacs which do not communicate with the outside since the region representing the larynx has not attained full development and lacks a lumen. Later on the folds of the glottis, fused together up to this moment, separate and a communication between the lungs and the pharynx is thus established; the tadpole begins to use the lungs, swimming to the surface of the water to obtain air.

The presence of large numbers of Mycobacterium in the lungs of young tadpoles which are still breathing through their gills shows conclusively that the bacilli had not been inhaled, but that they had been "dumped" into the lung cavity by migrating macrophages the nuclei of which appear among the bacilli (figure 7). Migration of the macrophages into the lungs does not cease after these organs have started functioning, for they are seen within the lung wall which appears still thinner since the lungs are now distended with air. However, collections of bacilli and degenerating macrophages are not seen in the lung cavity because they are promptly removed through the action of the cilia of low columnar epithelial cells which represent the bronchial epithelium of the mammal. Even though the older tadpoles breath through the lungs the penetration of bacilli from the pharynx into these organs is highly improbable since the necessary mechanisms to prevent the passage of food into the respiratory system are already operative.

Contrary to our suppositions the presence of large numbers of Myco-

bacterium in the walls of the lungs does not lead to the formation of tubercles in these organs. There is no question that macrophages degenerate within the lung tissues (figure 6) and that numbers of bacilli are thus released, but they are apparently phagocytized by young macrophages which migrate into the lung cavity after crossing the flat epithelium forming the inner lining of the rudimentary alveoli. The latter are shallow outpocketings of the lung wall, which, in addition to the ciliated cells, contains numerous smooth muscle fibres. Neither muscle fibres nor ciliated cells occur in the alveoli. Removal of desquamated cells, macrophages and bacilli through ciliary action may be relatively easier in the tadpole than in the mammalian lung since there are no long alveolar and bronchial passages. In this respect, the lung of the tadpole is an important means for the elimination of Mycobacterium. Whether lung tubercles arise in the frog, in which the lungs have thicker walls and a somewhat more complex structure, is a point which requires investigation.

FORMATION AND STRUCTURE OF THE TUBERCLES

In the interpretation of the lesions produced by the *Mycobacterium marinum* in the organs of the tadpole, it must be remembered that we are dealing with a larva, that is, a stage of development which is intermediate between the embryo and the adult. Under such conditions it would be logical to expect certain differences in the formation and structure of the tubercles, yet the reaction of the tissues of the tadpole to the infecting agent is remarkably similar to that of the mammalian tissues. As is the case in the latter, the slight differences to be observed in the tubercles are due less to variations in the character of the inflammatory reaction than to differences in the structure of the organs in which the lesions

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PLATE 2

All figures in this plate are unretouched photomicrographs of sections stained with hematoxylin and eosin.

Fig. 8. Frontal section of the entire tadpole showing organs of the abdominal cavity. Numerous tubercles of various sizes are seen in the liver, l; g, gills; i, intestine; k, kidney (mesonephros); l, liver; m, buccal cavity; s, stomach; t, root of the tail.

Fig. 9. Small tubercle in the submucosa of the intestine. Notice normal aspect of the mucosa. The submucosa appears thicker than in the normal areas at the level of the tubercle.

Fig. 10. Small tubercle in the pyloric region of the stomach. Some of the epithelial cells of the mucosa are undergoing degeneration, as well as the cells lining the glands next to the tubercle. The group of cells with clear cytoplasm in the mucosa at the right of the tubercle belong to the duct of a gland.

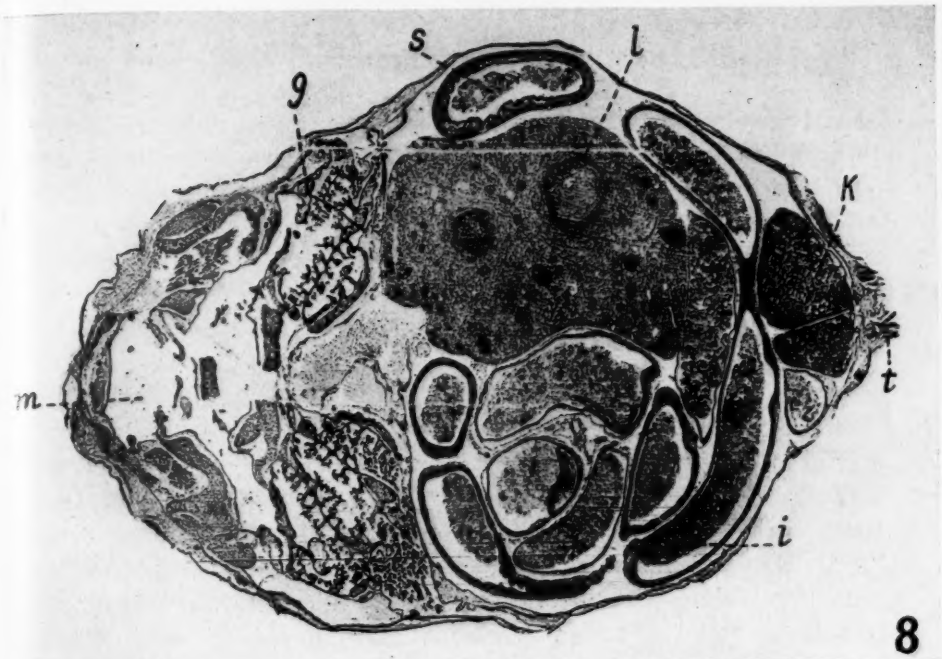


PLATE 2

develop. The formation of tubercles in the diverse organs in which they have been observed will be considered in the following paragraphs.

Intestine: Since the intestine is the portal of infection in tadpoles fed the Mycobacterium numerous tubercular lesions are to be found in this part of the digestive tract. In their earliest stages they consist of small accumulations of cells around bacilli presumably released by degenerating mucous cells and macrophages. In slightly later stages the number of cells has increased, and the conglomerate has become spherical. In every case the tubercles begin to develop in the submucosa, the mucosa in most cases does not seem disturbed or only to a slight degree.

Figure 5 shows a small accumulation of cells in the submucosa. The cell conglomerate consists of fibroblasts and roundish cells with a large nucleus and basophilic cytoplasm somewhat resembling lymphocytes. These round cells (m), some of which contain bacilli, we interpret as young mononuclear leucocytes (monocytes) migrated from the vessels. As already stated, in the tadpole this cell-type develops into the macrophage or histiocyte which wanders in the tissues. Bacilli also occur in the cytoplasm of the fibroblasts, but their presence in these cells may not be due to phagocytosis since in the living tadpole the connective tissue cells may withdraw some of their processes and form new ones, which may enclose the bacilli. A few cells with pyknotic nuclei, presumably fibroblasts, also occur in the area copied.

A larger tubercle from the submucosa of the intestine is illustrated in figure 9. The necrotic centre characteristic of the larger tubercles has not yet appeared in this case. The round deeply-stained nuclei we interpret as belonging to young monocytes which have migrated from the vessels.

As the growth of the tubercle proceeds a number of cells occupying its centre degenerate. In sections stained with the Ziehl-Neelsen technique the cell debris in the centre of the tubercle stains light pink or

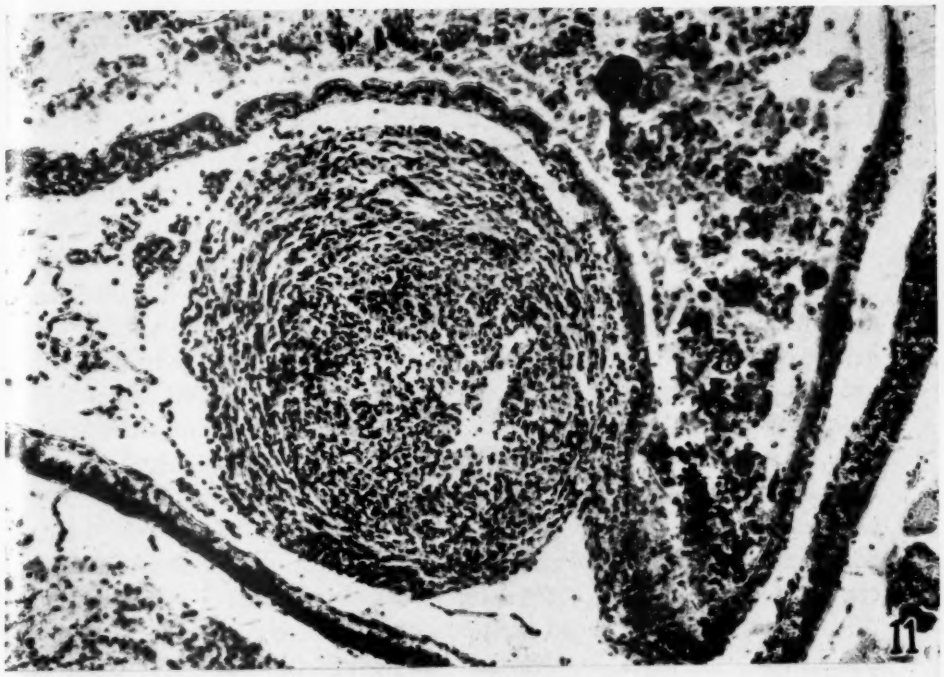
PLATE 3

All figures in this plate are unretouched photomicrographs of sections stained with hematoxylin and eosin.

Fig. 11. Large tubercle with necrotic centre developed in the submucosa of the intestine. The latter appears filled with food, masses of pigment and clumps of bacilli. The area of attachment of the tubercle to the submucosa is clearly seen at the right of the tubercle.

Fig. 12. Small tubercles in the portal of the liver. Sections of the hepatic ducts and branches of the portal vein seen in the figure.

Fig. 13. Large tubercle with necrotic centre; liver. The tubercle photographed is the largest of figure 8.



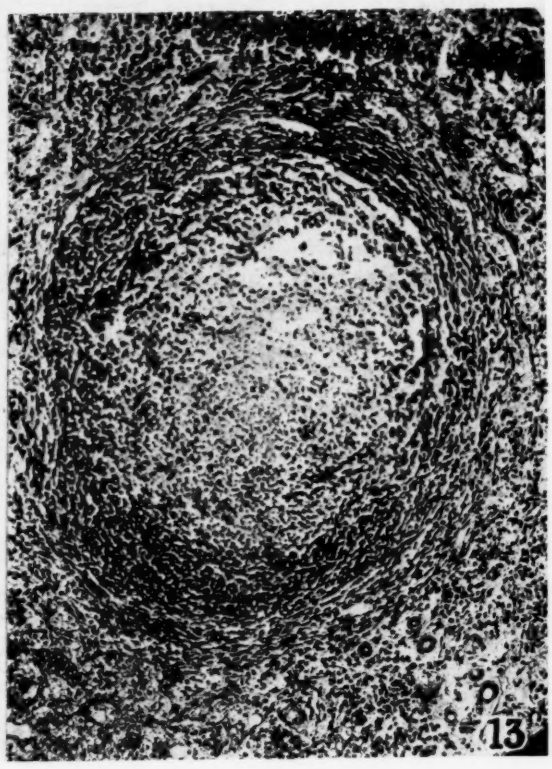


PLATE 3

pale lavender, and numerous bacilli are found in this area. Pyknotic nuclei and nuclear fragments also abound. Around the necrotic centre we find a fairly dense area consisting of elongated nuclei and numerous roundish cells. Some of the latter are macrophages resembling the epithelioid cells of the mammalian tubercle. They appear in different stages of degeneration and often contain bacilli. The elongated nuclei, also showing diverse stages of degeneration, belong to fibroblasts. As in the case of the mammalian tubercle there is apparently fibroblastic proliferation, though few or no mitoses were observed in support of this interpretation. In large tubercles the fibroblasts are arranged concentrically, and they form the outer layer of the tubercle (figure 11). As compared with the mammalian tubercle the corresponding structures of the tadpole show a more marked degree of fibroblastic hyperplasia, which may perhaps be explained on the assumption that the proliferative capacity of the fibroblasts is greater since they are still embryonic cells. The characteristic giant cells, usually but not always present in the mammalian tubercle, are absent in the tubercles of the tadpole, regardless of their location. Eosinophilic and neutrophilic leucocytes occur around the tubercles but as far as we have been able to see they do not contain bacilli.

Diverse stages of the formation of tubercles were also found in the mesentery. As in the case of the intestine the fibroblasts are also numerous around the tubercle. Numerous young macrophages are seen scattered among the connective tissue elements of the mesentery, suggesting that they may arise extravascularly in areas comparable with the milky spots of the mammalian mesentery.

Stomach: Tubercles in the stomach must be of rare occurrence since only one was observed in the tadpoles studied; it occurred in the submucosa of the pyloric region (figure 10). Its histological structure is similar to that of the tubercles of the intestine, but since the glands of the stomach extend through the submucosa and reach the inner muscle coat, the growing tubercle has displaced the glandular elements, some of which appear undergoing degeneration. As in the case of the intestine the rest of the mucosa appears intact, with the exception of a few degenerating ciliated cells, clearly seen in the figure. Since bacilli were never found within the gastric glands it does not seem likely that the infection started in the stomach. In all probability the bacilli reached the organ from some other area.

Liver: The largest tubercles were found in the liver in which they can

be seen in sections with the naked eye (figure 8). Furthermore, the tubercles in the liver are more numerous than in any other organ and their size ranges from small, spherical accumulations of cells to large tubercles with conspicuous necrotic centres (figures 8 and 13). The smaller or younger tubercles are found near the portal of the liver among the hepatic ducts and larger branches of the portal vein (figure 12).

In tadpoles raised in the laboratory on a diet of yolk of hard-boiled egg the liver cells are infiltrated with fat. The fat drops are of uneven size and do not merge to form a large drop; accordingly the nucleus remains in the centre of the cell or is slightly eccentric, and the pressure exerted by the fat stored in the cytoplasm on the nuclear wall changes the outline of the nucleus, which usually has a somewhat crenated aspect. The smallest tubercles in the liver are very similar to the intestinal tubercles, and they lack necrotic centres (figure 12). The latter begin to appear in medium-sized tubercles, attaining greater development than in the intestine. The reaction of the tissues to the Mycobacterium is relatively more marked in the liver than in the other organs, but this may be partly due to the presence of large numbers of reticuloendothelial cells in the liver. These cells move in large numbers toward the incipient tubercle and in so doing they may occlude the sinusoids, thus cutting off the blood supply to the liver cells which degenerate rapidly. Since the latter are loaded with fat drops they release the fat. The clear aspect of the necrotic centre in slides stained with the routine methods may be due to the presence of the liberated fat. Large numbers of bacilli occur within the centre as well as fragments of nuclei, some belonging to the degenerated macrophages, others to the dead liver cells. With further growth the tubercle compresses and kills the liver cells in the immediate vicinity. Around the necrotic centre there is a dense area formed by proliferated fibroblasts and numerous macrophages and monocytes, both healthy and undergoing degeneration. In some cases they contain numerous bacilli, which are released upon disintegration of the cell (figure 4). Outside the tubercle there is a layer of proliferated fibroblasts arranged concentrically, as in the intestine.

Spleen: Tubercles in the spleen were found only in one tadpole. The tubercles in these cases were small and lacked necrotic centres. They resembled closely the corresponding structures of the intestine. Bacilli in the spleen were observed time and again in the several tadpoles, but since tubercles are rare in this organ it is quite possible that the bacilli may be destroyed there if present in moderate numbers.

COMMENT

Any attempt to extend the results of the present study to the higher vertebrates and particularly to the mammals would seem unwarranted in view of the fact that the tadpole is the larva of a cold-blooded animal. Yet the study of tuberculosis induced by feeding in this form discloses certain features which deserve emphasis because they have been the subject of controversy in the field of mammalian tuberculosis.

Our investigations demonstrate beyond reasonable doubt that typical tuberculosis arises after ingestion of the bacilli and under conditions which preclude the penetration of the organism via the respiratory system. They also disclose that the intestinal barrier can be surmounted—in the absence of previous pathological changes—by a nonmotile microorganism, and that access to the mucosa is furnished by the normal process of discharge of the mucus by the goblet cells. The penetration of the bacilli in the empty goblet cells seems to be accidental, if we judge from the relatively small proportion of the cells containing them. Once the intestinal barrier has been surmounted the cell elements that constitute the defenses of the body are unable to cope with the infecting agent, for, although they phagocytize it and the cells in which it is contained, they are not successful in checking its spread. In fact, the macrophages which carry bacilli in their wanderings through the tissues and lymphatics become the most important agents in the spread of the disease. Considering the large numbers of bacilli in the tubercles it is evident that they grow and multiply within the latter; it is also quite possible that they reproduce within the infected mucous cells and perhaps also while in the cytoplasm of the macrophages. That the latter can kill the bacilli if present in small numbers is quite likely, but if too many of them have been phagocytized the reverse may happen, that is, the bacilli may slowly cause the death of the macrophage. (In this connection, however, the work of Sabin and Doan (8) should be cited. According to these observers the mononuclear phagocytic cells may be divided into two strains. The clasmatocytes phagocytize tubercle bacilli freely and fragment them, while the monocytes stimulated to metamorphose into the typical epithelioid and giant cells of the Langhans type retain the tubercle bacilli intact with power to survive and multiply over a considerable period of time. These observations were made on rabbits with bovine tubercle bacilli as the infecting agent.)

In very young tadpoles continuously fed the bacillus the infection is

fatal within a few days. In older tadpoles in which the leucocytes are already present in the blood the infection can be fought more successfully. Numbers of mononuclear leucocytes leave the blood-stream to enter the affected tissues. They closely resemble lymphocytes but are phagocytic whereas the latter, as shown by the Clarks in the living tadpole, lack the power of phagocytosis. We regard the phagocytic cells of the tissue as young monocytes. Their similarity with the lymphocytes is so striking that in the frog they have been regarded as arising from lymphocytes (Jordan (9) (10)). For our purpose further discussion of this point is unnecessary since we are concerned only with the type of blood cell which is capable of phagocytosis after leaving the blood-stream, not with its origin in the haemopoietic centres of the tadpole, located in the kidneys (mesonephroi) and, according to Jordan and Speidel (11), to some extent also in the spleen.

While numbers of monocytes leave the blood-stream and phagocytize bacilli and dead cells, thus becoming macrophages, they do not return to the blood-vessels after once engulfing the bacilli. This important point could be settled in the tadpole because the whole animal had been sectioned serially, and no cut leading to haemorrhage was made prior to fixation. If macrophages containing bacilli enter the intestinal capillaries one would expect to find them in the larger vessels and the cavities of the heart. Our search for such cells in the blood-stream has always led to negative results. We are forced to conclude, therefore, that the route followed by the macrophages containing bacilli must be a different one, either through the lymphatics or by way of the body cavity or both. We are aware that the early presence of tubercles in the liver would suggest the arrival of the bacilli to this organ through the portal vein, but we have never been able to see cells containing them in this vessel or in its main branches within the liver. On the other hand, it must be remembered that the tadpole lacks lymph nodes and that macrophages with bacilli within the lymphatics would not find any obstacle interposed in their path.

Finally, a point that deserves comment is the presence of large numbers of bacilli in the lungs at a time in which these organs have not started functioning and have no open communication with the pharynx. Along with the bacilli there occur numbers of nuclei belonging to the degenerating macrophages that transported them into the lung cavity. We have already indicated that the passage of macrophages from the intestine to the lung wall is anatomically possible since the tadpole lacks a dia-

phragm; but, since the lung has an efficient mechanism for the elimination of particulate foreign matter, we may ask ourselves whether this "dumping" of the bacilli is merely accidental or whether it constitutes an important route for the elimination of the pathogenic agent. In the functioning lung bacilli and macrophages are still seen in the lung wall, but very few or none occur in the cavity of this organ since they may have been eliminated through the activity of the numerous ciliated cells.

SUMMARY AND CONCLUSIONS

1. Tadpoles fed *Mycobacterium marinum* develop typical tuberculosis. The portal of the infection is represented by the goblet cells of the intestine after discharge of their mucus, the bacilli entering them in a more or less accidental manner. The goblet cells with enclosed bacilli undergo degeneration and are engulfed by tissue phagocytes (macrophages).

2. The macrophages with ingested bacilli wander about the submucosa of the intestine and may enter the lymphatics or pass into the body cavity. They slowly degenerate and their remnants are taken up by other macrophages which further spread the infection since they are apparently unable to kill the bacilli. Many macrophages arise from mononuclear leucocytes (monocytes) migrated from the blood-vessels or, as previously shown by the Clarks, in the tail of the living tadpole.

3. The absence of macrophages with ingested bacilli in the blood-vessels and heart, repeatedly verified through a study of serial sections of entire tadpoles, shows that the infection does not spread through the blood. The lymphatics and the body cavity are the main routes followed by the macrophages carrying the bacilli.

4. Numerous macrophages leave the intestine and enter the lung wall where they may degenerate and release the bacilli, which are taken up by other macrophages and "dumped" into the lung cavity. In young tadpoles in which the lungs are not yet functioning large numbers of bacilli and degenerated macrophages occur within the cavity of the lung. In older tadpoles with functional lungs, bacilli appear within the wall of these organs but both the macrophages and bacilli reaching the cavity are apparently eliminated through the action of the ciliated cells of the inner lining of the lung cavity.

5. Tubercles in various organs are described. Large tubercles contain distinct necrotic centres in which bacilli and fragments of degenerated nuclei abound. Around the necrotic centre there is a dense area occupied

by macrophages resembling the epithelioid cells of the mammalian tubercle, and proliferated fibroblasts. The latter are more abundant than in the mammal. Giant cells were never observed in any of the tubercles examined.

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COEXISTENCE OF LYMPHOCYTIC LEUKAEMIA AND FAR-ADVANCED PULMONARY TUBERCULOSIS[1]

Report of a Case

W. J. RYAN AND E. M. MEDLAR

The coexistence of infectious diseases of serious import and of leukaemic processes has led to a belief that leukaemia may be fundamentally dependent upon bacterial infection, that is, aetiologically leukaemia might be of an infectious nature. Bacterial agents of different kinds have been reported in connection with blood dyscrasias but more attention has been attracted to the tubercle bacillus as the aetiological agent for these dyscrasias than any other single type of bacteria. Reports on the association of the tuberculous infection with Hodgkin's disease and with myelogenous leukaemia are much more numerous than with lymphocytic leukaemia. Ryan (1) reported a case without necropsy of moderately advanced pulmonary tuberculosis which developed an acute lymphocytic leukaemia and died in a few weeks. Weil, *et al.* (2) reported a case with tuberculous cervical lymph nodes but without pulmonary involvement. Feigenbaum's case (3) had generalized miliary tuberculosis with but slight pulmonary involvement and it is doubtful if this case was one of lymphocytic leukaemia. Fischer's case (4) was one of chronic lymphocytic leukaemia and generalized miliary tuberculosis which developed subsequent to the onset of the leukaemic process. Parker, *et al.* (5) found evidence of tuberculosis in three out of thirty cases of lymphocytic leukaemia and in all three of these cases the tuberculosis was healed.

The case we report is of especial interest in that he had a clinically active far-advanced pulmonary tuberculosis with cavitation; he was under sanatorium treatment for over six months so that he could be carefully studied; he had a blood-picture typical of chronic lymphocytic leukaemia; and necropsy was performed.

[1] From the Summit Park Sanatorium, Pomona, New York, and the Hegeman Memorial Research Laboratory of the Metropolitan Life Insurance Company Sanatorium, Mount McGregor, New York.

Case Report

O. A., German-American, married, age 55 years, was admitted to the Summit Park Sanatorium on June 4, 1935, with the diagnosis of far-advanced pulmonary tuberculosis. Father died of pulmonary tuberculosis at the age of 31, and his wife succumbed to the same disease in 1931. The patient gave a

TABLE 1

Blood findings during sanatorium residence

DATE	ERYTHROCYTES		LEUCOCYTES						
	Total in millions	Haemoglobin	Total in thousands	Neutrophiles	Immature neutrophiles (100 counted)	Lymphocytes	Monocytes	Eosinophiles	Basophiles
		grams		*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
6/12/35	2.18	6.6	280	2 (5,600)	—	98	—	—	—
6/18/35	3.34	—	331	2 (6,600)	—	98	—	—	—
6/26/35	2.98	6.46	364	2 (7,300)	52 (3,800)	98	—	—	—
7/ 3/35	3.34	4.95	338	2 (6,800)	68 (4,600)	97	0.5 (1,700)	—	0.5
7/11/35	2.62	—	340	2 (6,800)	64 (4,300)	98	—	—	—
7/18/35	2.27	5.50	250	1.5 (4,000)	74 (2,900)	98	0.5 (1,200)	—	—
7/25/35	2.88	—	302	2 (6,000)	50 (3,000)	97	1 (3,000)	—	—
8/ 1/35	3.30	6.32	287	3 (8,600)	50 (4,300)	96	1 (2,800)	—	—
8/ 8/35	3.10	6.18	295	2 (5,900)	67 (3,900)	97	1 (2,900)	—	—
8/15/35	2.64	6.05	271	2 (5,400)	75 (4,000)	97	1 (2,700)	—	—
8/23/35	—	5.91	250	2 (5,000)	75 (3,700)	98	—	—	—
8/29/35	—	—	290	2 (5,800)	65 (3,800)	98	—	—	—
9/ 4/35	2.00	5.50	260	3.5 (9,300)	68 (6,300)	96	0.5 (1,300)	—	—
9/12/35	—	—	240	3 (7,200)	67 (4,800)	97	—	—	—
9/19/35	2.61	5.50	227	4 (9,100)	63 (5,700)	96	—	—	—
9/27/35	3.50	5.50	263	4 (10,500)	50 (5,200)	96	—	—	—
10/ 4/35	3.12	5.50	220	2 (4,400)	50 (2,200)	98	—	—	—
10/11/35	3.30	5.50	230	3 (6,900)	65 (4,500)	96	1 (2,300)	—	—
10/19/35	3.25	5.50	250	5 (12,500)	60 (7,500)	94	1 (2,500)	—	—
10/26/35	3.32	5.50	200	3 (6,000)	67 (4,000)	96	1 (2,000)	—	—
10/30/35	3.16	5.50	180	3 (5,400)	72 (3,900)	96	1 (1,800)	—	—
11/ 9/35	3.39	5.37	192	5 (9,600)	70 (6,700)	93	1.5 (2,700)	0.5	—
11/19/35	2.98	5.23	154	4 (6,200)	72 (4,500)	95	1 (1,500)	—	—
12/ 3/35	2.78	4.81	212	3 (6,400)	90 (5,800)	96	1 (2,100)	—	—
12/14/35	3.10	4.81	160	2 (3,200)	94 (3,000)	97	1 (1,600)	—	—

history of cough since 1929 and was suspected of being tuberculous, but no chest examination at the clinic was permitted until a few days before his admission. *Physical examination* revealed a very ill, emaciated, anaemic appearing patient. There was extensive disease throughout the entire left lung with a large cavity in the upper lobe. The right lung revealed physical signs in the

upper one-third. Palpation of the abdomen revealed a markedly enlarged spleen which extended to the midline and downward to the crest of the ilium. No demonstrable change in the size of the spleen was found subsequent to his admission. No palpable lymph nodes were found. Physical examination was otherwise essentially negative. *X-ray* of the chest demonstrated a very dense right hilum shadow with considerable soft nodular infiltrate throughout the lung. There was a large area of rarefaction in the left upper indicating probable cavity formation. During the patient's residence sputum was fairly copious and was persistently positive for tubercle bacilli (Gaffky V to VIII). The unusual *blood picture* (figure 5) found on the routine examination after the admission of the patient led us to a careful weekly study of the circulating blood. The results obtained are given in table 1.

The patient was strictly confined to bed from the date of his admission. Temporary improvement in his temperature and pulse rate took place during the first two months, but about the middle of August, 1935, two months after his admission, his temperature again rose and persisted at from 101° to 103°F. with a pulse rate of 110 to 130. The patient died on December 16, 1935.

Necropsy[2]

The essential gross findings were: Extensive tuberculosis of left lung, with a large cavity in the upper lobe and smaller cavities in the lower lobe; numerous small tuberculous foci in the right lung; enlarged peribronchial lymph nodes which on section did not appear tuberculous; pericardial effusion; obliterative pleuritis (bilateral); enlarged mesenteric lymph nodes; abundant reddish bone-marrow; enlarged spleen (9 x 6 x 4 inches) which did not appear to be tuberculous.

Microscopical examination of the lung tissue showed: The wall of the cavity was composed of fibrous tissue with marked lymphocytic infiltration in the outer portion (figure 4) and neutrophilic infiltration (figure 3) in the inner portion; tubercle bacilli were easily demonstrable in the inner surface of the cavities; in other portions of the lung there were caseous foci, typical tubercles with monocytes, giant cells and some lymphocytic infiltration, and considerable

PLATE 1

Fig. 1. Section from peribronchial lymph node showing typical healing tubercle. Note that lymphocytic infiltration of tubercle is no greater than in fig. 2. This lymph node showed several such tubercles. The remainder of the enlarged node was composed of closely packed lymphocytes similar to the condition surrounding the tubercle. × 300

Fig. 2. Healing tubercle from pulmonary tissue. Note fibrosis and lymphocytic infiltration which is no different from a similar tuberculous lesion in a nonleukaemic individual. × 300

[2] We are indebted to Dr. Wm. R. Strutton who performed the necropsy.

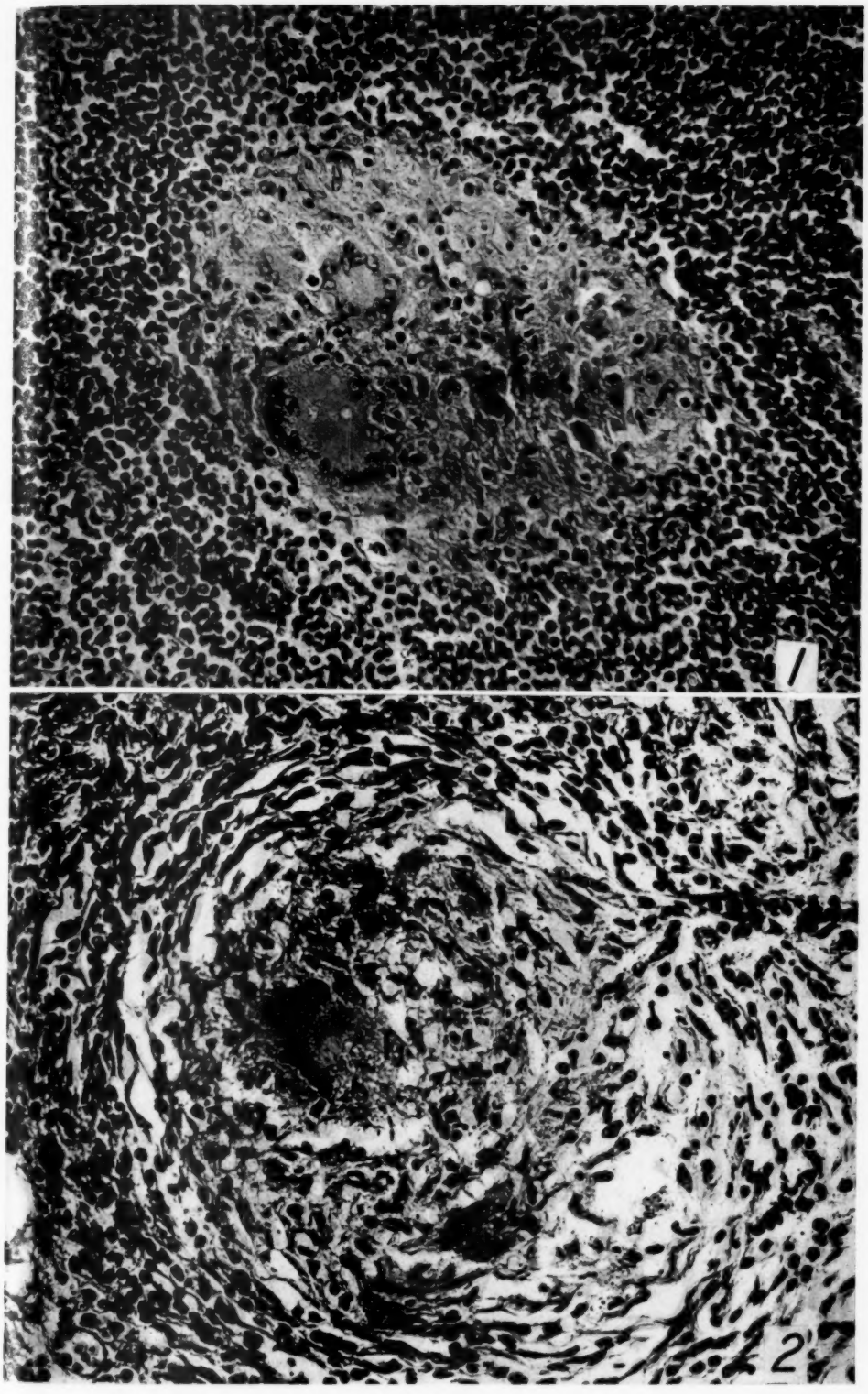

PLATE 1

areas of fibrous tissue which were infiltrated to a greater or lesser extent with lymphocytes; no tubercle bacilli could be found in these regions.

The peribronchial lymph nodes (figure 1) showed a few scattered tubercles with monocytes, giant cells and a moderate infiltration of lymphocytes. The tissue outside of the tubercles was closely packed with lymphocytes and there was a slight degree of infiltration of the capsules of the nodes with lymphocytes. A similar condition without tubercle formation was present in the mesenteric nodes.

Several sections of splenic tissue (figure 7) were examined and they all showed the pulp closely packed with lymphocytes. No evidence of tuberculosis was found. The malpighian corpuscles could be easily distinguished and did not appear to be involved in the leukaemic process. They appeared less cellular than the pulp.

The rib-marrow (figure 6) was very cellular and was devoid of fat. There were large irregular areas in which the cells were all of the lymphocytic type. Adjacent to and between such lymphocytic accumulations there was hyperplastic myelogenous tissue with the predominant cell being of the myelocytic type.

Sections of other tissues revealed nothing of particular note.

COMMENT

The coexistence in this case of typical lymphocytic leukaemia and of clinically active far-advanced pulmonary tuberculosis throws additional light upon the relation of leucocytes to the tuberculous process. The association of these two diseases is rare and according to Parker, *et al.* "in our experience malignant lymphoma of other types (not Hodgkin's disease) is never associated with *active* tuberculosis." While our case shows that *active* pulmonary tuberculosis and lymphocytic leukaemia can be associated, such a condition must be very rare as we could find in the literature but one comparable case.

In our case it is impossible to state whether the diseases occurred

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PLATE 2

Fig. 3. Inner wall of tuberculous cavity showing neutrophilic infiltration and fibrinous exudate. There were no lymphocytes in such locations. Tubercle bacilli were easily demonstrable in this purulent exudate. ×500

Fig. 4. The outer portion of the thick cavity wall taken from same section of tissue as fig. 3. Note fibrosis and abundant lymphocytic infiltration. In numerous areas the infiltration was even more intense than shown here. No other type of leucocyte was present and tubercle bacilli could not be demonstrated in such areas. × 500

Fig. 5. Blood film showing general picture of the circulating blood. There are 12 typical lymphocytes, 1 monocyte and 1 nonsegmented neutrophile. × 1000

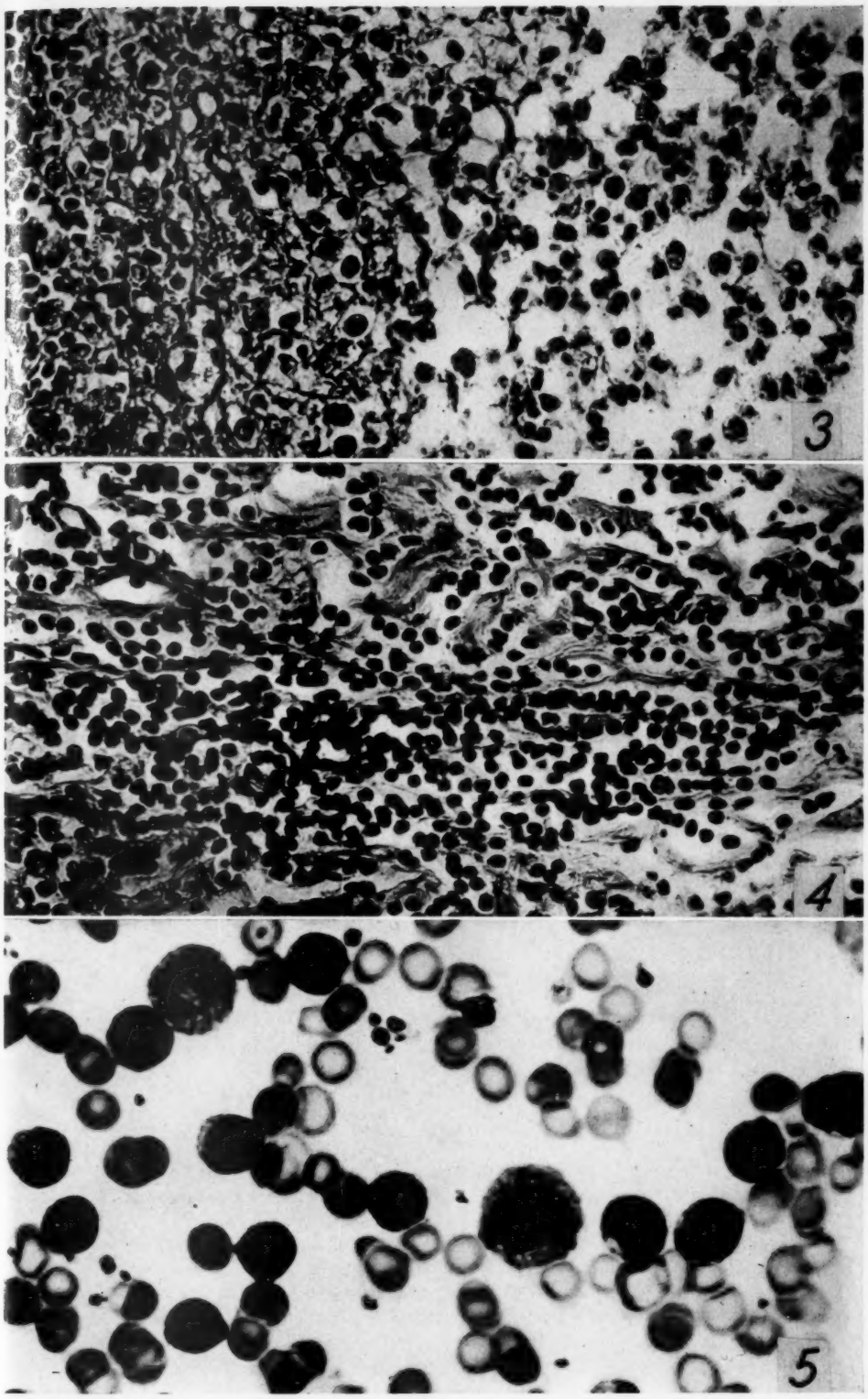


PLATE 2

simultaneously or whether one followed the other. No aetiological relationship of the processes can therefore be determined.

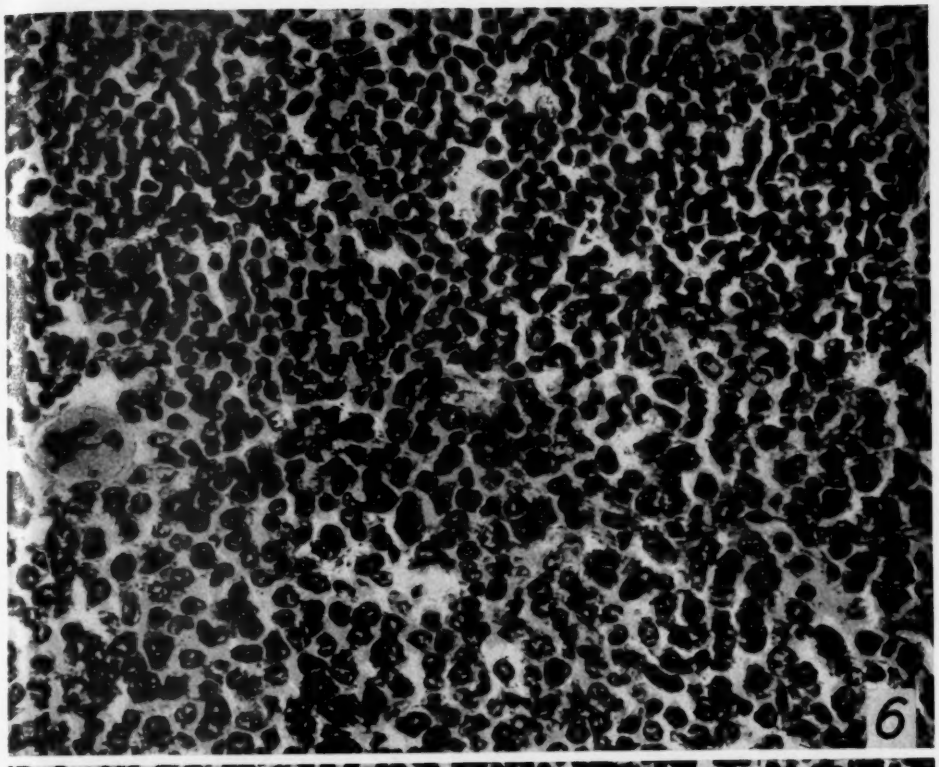
It is well known that in uncomplicated tuberculous cases a high percentage of lymphocytes is a favorable sign, yet in this case such an interpretation of the leucocytic picture would be erroneous. The blood contained from fifty to over one hundred times as many lymphocytes as normal and still there was an active progressive pulmonary tuberculosis. In such a condition one may regard the lymphocytes as being abnormal in function and hence unable to participate in the tuberculous process. If one may judge by the presence of lymphocytic infiltration, the majority of the tuberculous lesions did not differ essentially in this case from those in individuals without leukaemia. In some areas lymphocytic infiltration was so excessive that it appeared as if these cells were multiplying within the tuberculous foci. At least the lymphocytes were present in the same locations in the same type of tuberculous lesions as they are commonly found in uncomplicated tuberculosis. It is not possible to determine whether any abnormality of functional activity existed in these lymphocytes but at least they showed a tendency to imigrate to the locations where normal lymphocytes are commonly found.

Unless the lymphocytes in lymphocytic leukaemia are nonfunctional, then this case suggests that a lymphocytosis *per se* is not of prime importance in tuberculosis. We do not believe that any of the leucocytes which participate in infectious lesions are attracted to the site of infection by the bacteria *per se*. Rather we believe that the chemical damage produced in the tissues by the presence and growth of the bacteria is what is responsible for the leucocytic invasion. The nature of chemical damage produced determines the type or types of leucocytic infiltration found. One of us (6) in a previous communication has suggested that the different phases of the pathogenesis of tuberculosis are reflections of changes in the chemical structure within the foci of inflam-

PLATE 3

Fig. 6. Rib-marrow. Note solid sheet of lymphocytes in the upper part and of hyperplastic myeloid tissue in the lower portion of the picture. No evidence of tuberculosis was found. × 500

Fig. 7. Section of spleen. Note that the pulp (right half of picture) is heavily infiltrated with lymphocytes. The malpighian corpuscles have larger cells and do not seem to be particularly involved. A part of a malpighian corpuscle is shown in the left-hand side of the photograph. No evidence of tuberculosis was found in the spleen. × 500



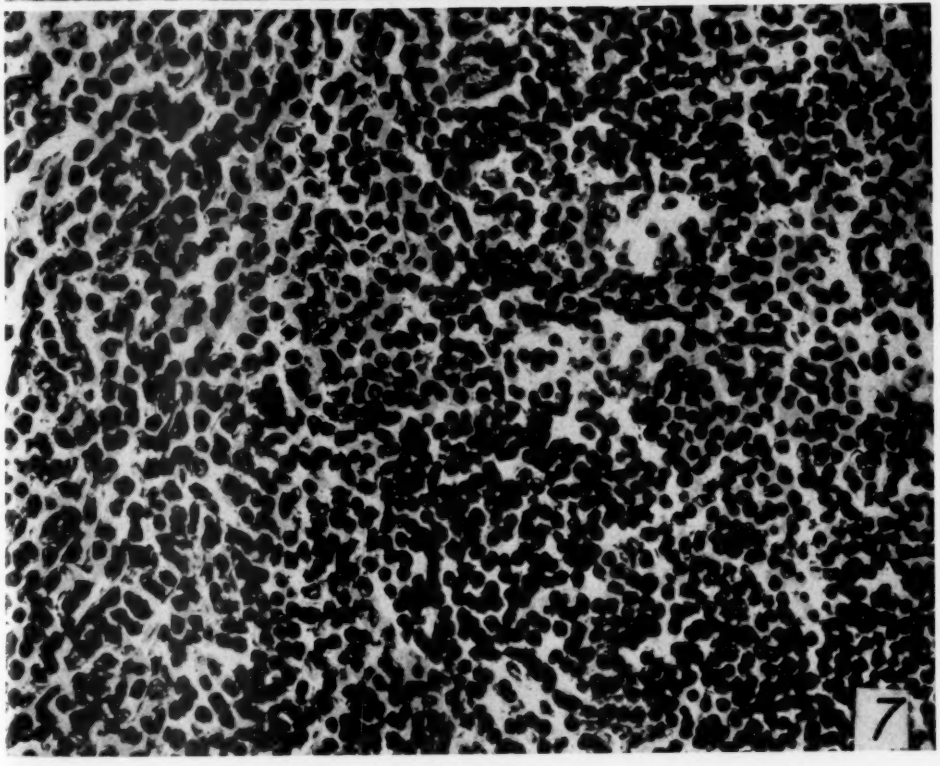


PLATE 3

mation. In other words, the lymphocyte, monocyte or neutrophile invades an area because the type of chemical alteration at a given point is such that they are functionally adapted to counteract it. If this be true then the case under discussion demonstrates the futility of attempts to produce artificial lymphocytosis in tuberculosis. Unless a physico-chemical condition exists within a tuberculous lesion which attracts lymphocytes they will not migrate into it no matter how many may be available in the circulating blood.

In previous communications (6) (7) one of us has stressed the part played by the neutrophile in certain phases of tuberculosis. A superficial inspection of the leucocytic counts given in table 1 would seem to contradict our previous assertions, since in this case the neutrophiles made up but 2 per cent to 5 per cent of the leucocytes. It will be noted however that in all but three counts the total number of neutrophiles was above 5,000, this being the upper limit of normal. In the column for immature neutrophiles it will be noted that 50 per cent to 94 per cent were of the nonsegmented nucleus type. Not only was the total number of neutrophiles increased but also the demand for neutrophiles was so great that there was a marked increase in the proportion of immature cells. In two cases of uncomplicated chronic lymphocytic leukaemia one of us (E. M. M.) had found the percentage of immature neutrophiles to be within normal limits. Whether this would hold for all of the uncomplicated cases of this type we cannot say. However, the marked difference between the leucocytic content of immature neutrophiles in the uncomplicated lymphocytic leukaemias we have studied and the case combined with tuberculosis is such that it seems reasonable to designate the active tuberculosis as the cause of the difference noted.

A study of the pulmonary lesions revealed the presence of neutrophiles in the usual locations for such cells, that is, the inner wall of cavities and caseous foci. Examination of the sternal bone-marrow showed myelogenous hyperplasia compatible with the circulating neutrophilic picture. Linking the pulmonary lesions, the marrow reaction and the circulating leucocytic picture, ample evidence is obtained to warrant the conclusion that the neutrophile functioned in the case under discussion in the same way that it does in uncomplicated tuberculosis.

The monocyte (total numbers) was also increased in the circulating blood and was found to be present in tuberculous lesions in the ordinary locations.

A survey of the case as a whole showed that the lymphocytic leukaemia had not changed the essential pathological picture of the coexisting active tuberculosis from that usually found in uncomplicated tuberculous infection. The circulating blood picture indicated not only the presence of lymphocytic leukaemia but also a serious disease process in which the neutrophile and monocyte were involved. The demonstration of clinically active pulmonary tuberculosis rendered an intelligent pathological interpretation of the significance of the neutrophilic and monocytic picture possible.

SUMMARY

A case in which lymphocytic leukaemia and active pulmonary tuberculosis coexisted is reported.

The independence of the two disease processes is suggested. Despite the presence of a lymphocytic leukaemia the tuberculous pathology was essentially the same as is found in uncomplicated tuberculous infection.

The participation of the lymphocyte in the tuberculous process seems to be dependent upon the conditions (probably chemical) within a lesion. The mere presence of a large number of lymphocytes in the circulation seems to have little if any influence upon the pathological condition within an active, caseating and cavitating process.

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THE EFFECT OF VITAMIN-A DEFICIENCY ON EXPERIMENTAL TUBERCULOSIS IN THE GUINEA PIG AND RABBIT[1,2]

MORRIS STEINER, MERIDIAN R. GREENE AND BENJAMIN KRAMER

INTRODUCTION

The influence of complete or partial lack of vitamins in the diet on the course of infection produced by the tubercle bacillus has interested us. Previous work has indicated that chronic deficiency of vitamin C appears to hasten the development of experimental tuberculosis in the guinea pig, while a deficiency in vitamin D in rabbits seems to have no effect on the tuberculosis produced in this animal (1). Since the recognition by McCollum and Davis (1913) (2) of the existence of a fat soluble vitamin necessary for growth, much work has accumulated to indicate that vitamin A plays a rôle in the resistance of the body to infection. McCollum (1917) (3) first drew attention to the susceptibility of rats to respiratory infection when fed on diets deficient in fat soluble vitamin. Later, E. Mellanby (1919) (4) showed that puppies under similar dietetic conditions often develop bronchopneumonia. Green and Mellanby (1928) (5) in an attempt to differentiate the effects of vitamin D and those of vitamin A were able to show that rats on diets deficient in vitamin A alone, developed a high percentage of lethal infections. As a result of their work they gave the name "anti-infective" vitamin to vitamin A. Further work by Mellanby and Green (1929) (6) indicated that clinically the administration of diets rich in vitamin A had a beneficial influence both in the treatment and prevention of puerperal sepsis.

Wolbach and Howe (1928) (7) have shown that keratinization of normal epithelium occurs in the respiratory, alimentary and gastrointestinal tracts, in the eyes and periocular glands in guinea pigs on vitamin-A deficient diets. In view of this finding it has been suggested that bacterial invasion may occur because of the interference with the normal healthy structure of the mucous membranes.

In these experiments it was planned to investigate the influence of

[1] From the Pediatric Research Laboratory, the Jewish Hospital of Brooklyn, New York.
[2] This work was aided by a grant from Mead Johnson and Company.

vitamin-A deficiency in guinea pigs and rabbits infected with tubercle bacilli. Very little work has been done on experimental tuberculosis in guinea pigs and rabbits maintained on rations depleted of vitamin A. Smith (1923) (8) found no difference in the amount of tuberculosis in guinea pigs fed on a diet deficient in vitamin A and in control animals receiving codliver oil in addition to the basal diet. His basal diet apparently was deficient in both vitamins A and D. He was unable to show any beneficial effects as far as the tuberculous process was concerned in infected animals fed normal diets and those receiving codliver oil in addition. He later (1925) (9) showed that rats infected with tubercle bacilli on adequate diets were about one-sixth as tolerant to tuberculoprotein as the noninfected controls, whereas rats maintained on a vitamin-A deficient diet and infected with tubercle bacilli were about one-fortieth as tolerant to tuberculoprotein as noninfected controls.

Finkelstein (1932) (10) followed the course of tuberculosis in albino mice which were on a vitamin-A deficient diet and then infected with a bovine strain of tubercle bacilli. The tuberculous process appeared to progress more rapidly in the vitamin deficient animals than in the controls.

Otero, Koppisch and Oxtmayer (1934) (11) were able to show that tuberculosis did not develop in rats on an adequate diet nor on one deficient in vitamin A after inoculation with human or bovine strains of tubercle bacilli. However, when an avian strain of the tubercle bacillus was used, tuberculosis developed in both groups but the disease progressed more rapidly in the animals depleted of the vitamin.

The problem which presented itself was to secure animals in which manifest signs of vitamin-A deficiency could be produced and which also could be infected with tubercle bacilli. Wolbach and Howe (7) have shown that vitamin-A deficiency can be produced in the guinea pig, although it is doubtful whether xerophthalmia, the common clinical manifestation of this deficiency, develops. Xerophthalmia, however, can be produced in rabbits on vitamin-A deficient diets and, since both of these animals show marked susceptibility to tuberculous infection, these two animals were used. Although we were able to produce vitamin-A deficiencies in both of these animals, it was difficult to maintain them over a long period of time, because the experimental diet, although theoretically adequate as regards all the needed known dietary factors, was a diet foreign to this species, since both guinea pigs and rabbits are herbivorous animals. A further discussion of this factor will be presented below.

PROCEDURE

Animals: Guinea pigs and rabbits of various breeds were used. All were obtained from the same farms.

Two rabbits or 6 guinea pigs of the same sex were kept in a cage. The cages were made of metal with a wire-mesh floor-screen over a removable tray. Each week the cages were soaked in 5 per cent cresol solution and thoroughly scrubbed. The temperature of the animal rooms, which were large and well ventilated, was maintained at 70–80°F. for the guinea pigs and at 60°F. for the rabbits.

The diet:

Vitamin-A deficient	per cent
Rolled oats	20.0
White corn meal	41.5
White mashed turnip	33.0
Brewer's yeast[3]	3.0
Calcium carbonate	1.5
Sodium chloride	1.0
Viosterol[3] 15 drops per kilo of ration	

Vitamin A	per cent
Rolled oats	17.0
White corn meal	39.5
White mashed turnip	33.0
Brewer's yeast	3.0
Calcium carbonate	1.5
Sodium chloride	1.0
Butter fat	5.0
Viosterol 15 drops per kilo	

Thirty-three gm. of turnip were mixed with 67 gm. of dry mixture. Multiples of this proportion of the constituents were given, the amount depending upon the number of animals in a cage. The dry mixture was prepared weekly and the turnips were ground twice a week and kept in the refrigerator. The diet was fed *ad lib.* Filter paper clippings were given for additional roughage. Freshly distilled water was given daily and iodine solution was added to this once a week. In addition, the guinea pigs were fed 5 cc. of fresh orange juice 6 times weekly. The amount of vitamin A in this quantity of orange juice did not prevent the condition of avitaminosis from developing and adequate protection against scurvy was assured. It was not thought necessary to give the orange juice to the rabbit as this animal is apparently not susceptible to scurvy.

A few guinea pigs were maintained on a diet normal for this animal. This consisted of rolled oats, 3 parts; wheat bran, 1 part; sodium chloride, 1 per cent; and calcium carbonate, 1.5 per cent. Alfalfa hay was provided. Fresh cabbage leaves were given 4 times a week.

The guinea pigs did not take kindly to the diet even though the basal diet supplemented with butter fat contained all the needed known die-

[3] Supplied through the courtesy of Mead Johnson and Company.

tary factors. It is doubtful if even those who could be made to take it would surive the normal life-span of a guinea pig. The lack of sufficient roughage, as is usually supplied by hay, appears to be the chief obstacle in maintaining herbivorous animals on experimental diets in a normal manner. Only those animals living after 5 weeks on the diet were used in the data of the experiment. Until this time deaths occurred in equal numbers in both groups, the one receiving the vitamin and the one being deprived of this factor. The mortality during this preliminary period was about 50 per cent. The pathological findings of the experimental animals will be discussed later.

Rabbits progressing normally on either the experimental or control diet frequently developed a sudden diarrhoea and died within a day or two. As coccidia were usually found in the faeces, a latent infection was apparently flared up by the lack of sufficient roughage in the diet. In spite of many attempts, no adequate substitute for hay could be made.

Tuberculin tests: At the onset of the experiment all guinea pigs gave negative dermal reactions when injected intracutaneously with 0.1 cc. of 5 per cent Old Tuberculin. Rabbits were not skin tested.

Infection of animals: The bovine strain, C3, obtained from the New York Department of Health, was used for inoculating the rabbits. Weighed, normal saline suspensions of the organism grown for 2 weeks on Petroff's glycerine-egg media were used. The guinea pigs were inoculated by the enteric route with sputum obtained from open cases of pulmonary tuberculosis.

Pathological procedure: Each animal was autopsied. The scoring for tuberculosis was adapted from the method of Petroff and Steenken (1930) (12), the involvement being graded from 1-plus to 4-plus according to its extent and severity.

After fixation in 4 per cent formalinized saline, sections were imbedded in paraffin, sectioned and stained by the hematoxylin-eosin method. Sections were also stained for 45 minutes at 56°C. in Neelsen's carbol-fuchsin and destained and counterstained in Gabbett's solution. These were then examined for the presence of tubercle bacilli.

Statistical method: The weights and survival time were analyzed by a special statistical method (R. A. Fisher's *Statistical Method*, page 107, Oliver and Boyd, London, 1930). As the method has already been described in detail in the first paper of this series (1), it is sufficient to say that when the value of P is .01 or less the difference between the means of the comparable series is statistically significant.

PROTOCOLS OF THE EXPERIMENTS

Group1: Nontuberculous guinea pigs: Six animals on the diet deficient in vitamin A, 7 animals receiving the basal diet supplemented with the vitamin and 4 animals on a normal guinea-pig diet were used.

TABLE 1

Summary of statistical analysis of weights and survival periods in guinea pigs on vitamin-A deficient and control diets

	WEIGHT MEAN IN GRAMS AT				SURVIVAL MEAN IN DAYS
	Onset	5 weeks	9 weeks	Death	
−A only	344	363	319	363	56
+A only	325	335	411	492	94
P	.36	.24	.14	<.01	<.01
Nor. only	327	514	598	671	100
+A only	325	335	411	492	94
P	>.9	<.01	<.01	<.01	
Nor. tb*	332	403	479	514	79
Nor. only	327	514	598	671	100
P	.64	.013	.019	.025	
Nor. tb*	332	403	479	514	79
+A tb	325	346	369	339	81
P	.503	.023	<.01	<.01	
+A tb*	325	346	369	339	81
+A only	325	335	411	492	94
P	1.0	.57	<.01	<.01	
−A tb*	345	349	311	305	68
−A only	344	363	319	363	56
P	>.9	.46	.83	.706	.12
−A tb*	345	349	311	305	68
+A tb*	325	346	369	339	81
P	.01	.82	<.01	.11	<.01

−A = basal diet alone.
+A = basal diet + 5 per cent butter fat.
Nor. = normal guinea-pig diet.
* = fed tuberculous sputum.
P = statistic, significant when less than .01.

Pathology: (*a*) *Weights and survival period:* Animals on a vitamin-A deficiency were maintained for 40 to 100 days when the experiment was terminated. As noted by Wolbach and Howe (1928) (7), the only ex-

ternal signs of the deficiency were a cessation of growth and weight loss. These animals died at a significantly earlier time than those receiving the supplemented basal diet. The guinea pigs depleted of the vitamin also weighed much less at death than their corresponding controls (table 1).

A second set of control animals (numbers 108–1,2,3,4) had been placed on a normal guinea-pig diet. These animals gained weight steadily and were in excellent health. They thrived better than the group on the basal ration supplemented with the vitamin. Their weights were significantly greater from the third week to the termination of the experiment when both series were killed (table 1).

(*b*) *The deficiency:* All sections of the trachea of guinea pigs on the vitamin depleted diet showed either a complete or partial replacement of the normal columnar epithelium by the squamous type of cell. In the series of 6 animals, the pelves and ureters of two were swollen, thickened and contained a gritty and pasty material. A bilateral hydronephrosis resulted. The bladder contained similar masses and the walls were thicker than normal. These findings did not occur in the animals receiving vitamin A. Cloudy swelling of the cornea as described by Boock and Trevan (1922) (13) was not found in these animals nor in the larger experimental group that follows.

(*c*) *Intercurrent infections:* Five of 6 animals on the depleted ration showed pneumonia at autopsy. This finding occurred in 2 of 7 animals on the ration supplemented with butter fat and in none of 4 on the normal herbivorous diet. These uninoculated animals were in the same room but not in the same cages with tuberculous guinea pigs and no cross infection resulted.

(*d*) *Summary:* Animals on the diet depleted of the vitamin died significantly earlier than those receiving this factor, and pneumonia was present in most cases of the avitaminosis. The vitamin-A deficient guinea pigs showed keratinization of the tracheal epithelium; two showed hydronephrosis.

Group 2: Tuberculous guinea pigs: Twenty-five guinea pigs on the basal diet, 22 on the same ration supplemented with 5 per cent butter fat as the source of vitamin A and 18 on a normal guinea-pig ration were fed .25 cc. of heavily infected sputum 5 times weekly with a tuberculin syringe. Feeding was begun when they were placed on their respective rations.

(*a*) *Weight and survival period of normal diet animals:* Tuberculous

animals on a normal guinea-pig diet weighed significantly less than non-infected animals on normal diets. The survival period was not calculated as the tuberculous animals were killed at various periods for pathological study.

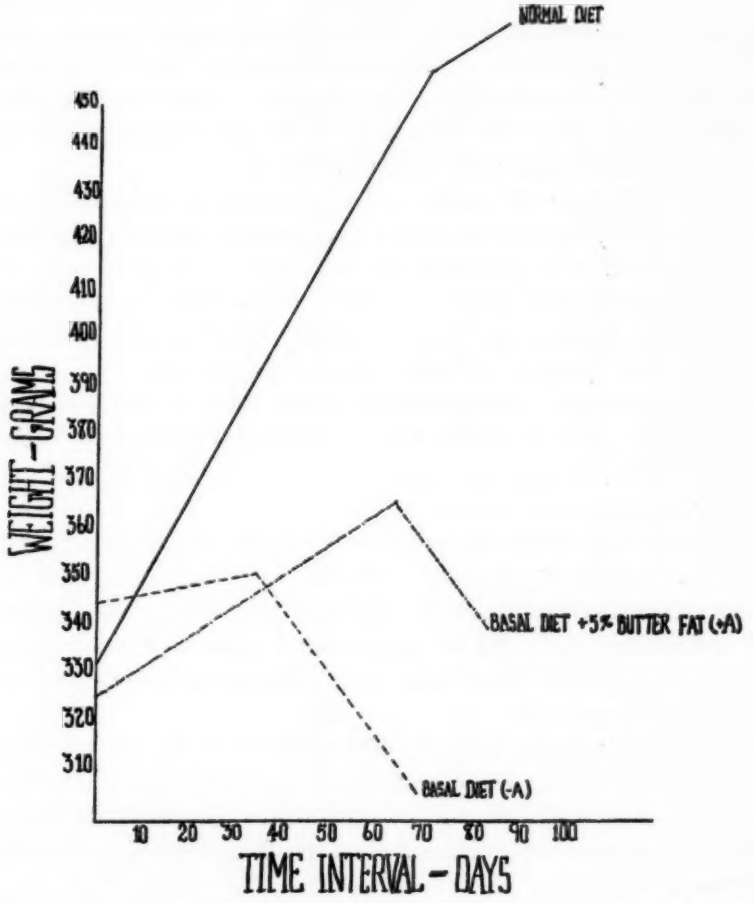

CHART 1. Mean average weights of tuberculous guinea pigs on normal diet; basal diet + 5 per cent butter fat (+ A); basal diet alone (− A)

(*b*) *Weight and survival period of experimental animals:* Tuberculous animals on the basal diet supplemented with 5 per cent butter fat weighed significantly more than tuberculous animals on the basal diet. At 5 weeks there was no significant weight difference but at 9 weeks the control animals weighed more. There was a significant difference in

weights between the infected animals receiving the basal diet and 5 per cent butter fat, and the infected animals on a normal diet, the latter animals weighing more at the end of the experiment.

The mean average survival period of the vitamin-A deficient animals was 68 days while that of those receiving the 5 per cent butter fat was 81 days. This difference in survival period was significant since P was less than .01. However, there was no significant difference in the survival period between the infected and noninfected animals on the deficient diet (table 1).

(*c*) *The deficiency:* Metaplasia of the normal columnar tracheal epithelium occurred in most of the vitamin-A deficient guinea pigs. Sixteen of 25 animals had dilatation of the upper portion of the ureters and pelves. In some, calculi were found. These were usually present in the upper portion of the ureter and pelvis. In several cases unilateral or bilateral hydronephrosis occurred. A more extensive study of this condition is now being undertaken (table 2).

(*d*) *Secondary infections:* Seventeen of 25 infected, depleted guinea pigs showed pneumonia at autopsy as compared with 3 of 22 animals in the control group.

(*e*) *Tuberculosis:* Eleven out of 21 animals (52 per cent) receiving the diet deficient in vitamin A had generalized tuberculosis, while 10 out of 21 control animals (48 per cent) on the basal diet plus 5 per cent butter fat showed similar involvement. (Animals 93–1 and 5, 95–3 and 98–5 were not included in the tuberculosis score as they lived less than 45 days and died of secondary pneumonia.) Histological study showed the same type of involvement in both groups but, as pointed out above, the vitamin-A deficient animals had a significantly shorter survival period than their corresponding control animals. When the experimental period was subdivided into 2 periods of 60 to 80 days and 80 to 100 days, it was found that 6 of 15 vitamin-A deficient animals had generalized tuberculosis as compared with 5 of 10 control animals in the first period, whereas in the second period (80 to 100 days) 5 out of 6 deficient animals had generalized tuberculous involvement as compared with 5 out of 12 control animals. Apparently, the lack of vitamin A did not hasten the development of tuberculosis in the animals succumbing early in the experiment.

In the third group of tuberculous animals, that is, those fed on a normal guinea-pig diet and infected with tuberculous sputum, only 5 out of 18 animals (27 per cent) had generalized tuberculosis as compared

TABLE 2

Autopsy findings in kidneys and trachea of vitamin-A deficient and control animals

ANIMAL NUMBER	KIDNEY (GROSS)	EPITHELIUM TRACHEA (MICROSCOPIC)	SURVIVAL IN DAYS
Experimental			
92–1	Early bilateral hydronephrosis	–	61
92–2	0	Squamous	62
92–3	Early unilateral hydronephrosis	Modified columnar	89
92–5	Bilateral hydronephrosis, gritty material in pelvis	Squamous	60
92–6	Bilateral hydronephrosis	Squamous	71
93–1	0	Modified columnar	43
93–3	Bilateral hydronephrosis	Squamous	75
93–4	Bilateral hydronephrosis, gritty material in pelvis	Squamous	71
93–5	0	Modified columnar	46
94–1	Left ureter slightly swollen	–	86
94–4	Very early hydronephrosis	–	67
94–5	0	–	64
95–1	Bilateral hydronephrosis, putty-like masses in pelvis, upper portion of ureter markedly swollen	–	62
95–2	Bilateral hydronephrosis	Squamous	87
95–3	0	Columnar	42
95–5	0	Columnar	41
96–2	Unilateral hydronephrosis	Squamous	72
96–3	0	Modified columnar	61
96–4	0	–	77
96–5	Beginning hydronephrosis, gritty material in right ureter	–	100K
96–6	Beginning hydronephrosis, gritty material in both pelves	Modified columnar	99K
97–1	0	Squamous	57
97–2	Bilateral hydronephrosis	–	94
97–4	Early bilateral hydronephrosis—upper ½ both ureters swollen	–	69
97–6	Bilateral hydronephrosis, gritty material in pelvis and upper ureter	Squamous	58
Controls 98–1 to 102–6	0	Columnar	81

– = mucosa unsuitable for microscopic study.
K = killed.
Experimental = vitamin-A deficient animals.

to 11 out of 21 vitamin-A deficient animals and 10 out of 21 control animals (basal diet + 5 per cent butter fat). The animals in this group

TABLE 3A

Relative amount of tuberculosis and survival time in vitamin deficient and control guinea pigs

ANIMAL NUMBER	LUNG	LIVER	SPLEEN	SMALL INTESTINE	CAECUM	COLON	GROSS TB. SCORE	SURVIVAL
Experimental								
92-1	1+*	3+*	2+*	0	0	0	3+	61
92-2	1+; Pn	0	1+*	0	0	0	1+	62
92-3	2+; Pn	3+	3+	2 ulcers*	0	0	4+	89
92-5	1+; Pn	0	0	0	0	0	1+	60
92-6	1+; Pn	2+*	3+*	0	Ulcer*	0	3+	71
93-1	0; Pn	0	0	0	0	0	0	43
93-3	0; Pn	2+	2+	1+*	0	0	2+	75
93-4	0; Pn	2+*	1+*	0	0	0	2+	71
93-5	0; Pn	0	0	0	0	0	0	46
94-1	1+	3+*	3+*	1+*	0	0	3+	86
94-4	2+; Pn	0	1+*	1+*	0	0	2+	67
94-5	0; Pn	0	1+	0	0	0	1+	64
95-1	3+*; Pn	0	2+*	0	0	0	2+	62
95-2	0	1+	1+	2+*	0	0	1+	87
95-3	0; Pn	0	0	0	0	0	0	42
95-5	0; Pn	0	0	0	0	0	0	41
96-2	0; Pn	2+	2+*	2+*	0	0	2+	72
96-3	1+*; Pn	–	1+	3+; 3+*	0	0	2+	61
96-4	2+	4+*	4+*	1+*	0	0	4+	77
96-5	3+; Pn	3+	3+*	3+; 2+*	0	0	4	100K
96-6	2+*	2+*	3+*	0	2+*	0	3+	99K
97-1	4+*; Pn	2+*	2+*	2+*	0	0	3+	57
97-2	3+; Pn	3+	2+*	0	0	0	4+	94
97-4	1+*	2+*	3+*	0	0	0	3+	69
97-6	3+; Pn	1+	1+*	1+*	0	0	3+	58
Control								
98-1	3+*	4+	4+*	4 ulcers	3+*	0	4+	96K
98-2	0	0	0	0	3+*	0	1+	94K
98-3	1+; Pn	1+	2+	3+; 2+; 1+*	0	0	2+	75
98-4	1+	0	1+	3+; 3+; 2+*	0	0	1+	96K
98-5	0; Pn	0	0	0	0	0	0	39
99-1	1+	0	1+*	1+*	0	0	1+	67K
99-2	3+*	4+*	4+*	1+*	1+*	0	4+	62K
99-3	1+	3+	2+*	2+*	0	0	3+	71K
99-5	1+*	2+*	2+*	0	0	0	3+	88K
99-6	1+	0	1+	0	0	0	1+	88K
100-2	2+*	2+	2+*	3+*	3+*	2+	3+	67K
100-3	0; Pn	0	1+	0	0	0	1+	78K
100-4	2+*	4+*	4+*	1+*	0	0	4+	78K
101-1	1+	0	1+	3+; 2+*	3+*	0	2+	62K
101-2	1+	0	1+	3+*	0	0	2+	88K
101-3	2+*	0	2+*	0	0	0	2+	88K
101-4	1+*	0	2+*	0	0	0	2+	88K
101-5	0	3+*	3+*	3+*	0	0	3+	71K
102-1	2+*	3+*	4+*	0	0	0	4+	95K
102-2	2+*	3+	3+*	1+*	1+*	0	4+	93
102-3	2+	0	1+*	0	0	0	2+	97K
102-6	1+*	1+*	2+*	3+; 2+*	0	0	3+	99K

* Tubercle bacilli found; Pn = pneumonia; experimental = vitamin-A deficient animals; control = basal diet + 5 per cent butter fat.

System of scoring explained in text.

were killed so that their survival period would correspond to the vitamin-A deficient group. The nutritional status of these animals was far superior to that of both experimental groups.

In the intestinal tract, 13 of 21 depleted guinea pigs had tuberculous lesions. These were present mostly in the ileum. One animal had tuberculous ulcer in this region and a second showed an area of ulceration in the caecum. Among the control group the incidence of lesions was the same but there was slightly more involvement in the caecum and colon. One animal receiving the vitamin had four ulcers in the small

TABLE 3B

Relative amount of tuberculosis in guinea pigs fed normal diets infected by sputum

ANIMAL NUMBER	LUNGS	LIVER	SPLEEN	SMALL INTESTINE	CAECUM	COLON	GROSS TB. SCORE	SURVIVAL TIME
103-1	1+	0	3+	0	0	0	2+	62K
103-2	2+	0	2+	3+	0	0	2+	99K
103-3	+	0	+	2+	0	0	2+	67K
103-4	+	0	2+	0	0	0	2+	78K
103-5	2+	3+	+	0	0	0	3+	71K
103-6	2+	+	3+	+	0	0	3+	99K
120-1	2+	0	+	+	0	0	2+	70K
120-2	0	0	+	0	0	0	1+	70K
120-3	0	0	+	0	0	+	+	87K
120-4	0	0	0	+	0	0	1+	77K
120-5	0	0	0	0	0	0	0	65K
120-6	0	0	+	0	0	0	1+	74K
143-1	Pn	4+	2+	3+	+	0	4+	66
143-2	0	0	0	0	0	0	1+	73K
143-3	2+	2+	2+	0	0	0	3+	73K
143-4	0	0	2+	+	0	0	1+	91K
143-5	4+	2+	3+	2+	0	0	4+	91K
143-6	0	0	+	0	0	0	1+	91K

K = killed.

intestine. However, the involvement of the intestines for the most part consisted of early or moderately advanced tubercles.

In the group of animals on the normal guinea-pig diet, 8 out of 18 animals had definite gross intestinal lesions, 2 of which were advanced, but no gross ulcers were found (tables 3 A and B).

Group 3: Nontuberculous rabbits: Seven rabbits receiving the diet supplemented with vitamin A and 3 animals on the basal diet alone were used.

Pathology: The animals on the vitamin-A deficient ration had a

TABLE 4

Significance of the mean weights of comparable groups of rabbits in vitamin-A experiment

GROUP	TIME	WEIGHT MEAN (GMS.)	DIFFERENCE	t	n	P
−A	Onset	1043				
+A		1049	6	.27	8	.79
−A	3 weeks	828				
+A		1153	325	5.81	8	< .01
−A	6 weeks	970				
+A		1278	308	3.16	8	.014
−A	Death	1003				
+A		1396	293	1.5	8	.16
−A	Onset	1043				
−A tb		1092	49	7.92	11	.44
−A	3 weeks	828				
−A tb		1033	205	3.66	11	< .01
−A	6 weeks	970				
−A tb		1012	42	.42	11	.68
−A	Death	1003				
−A tb		990	13	.13	11	.89
+A	Onset	1049				
+A tb		1096	48	.97	15	.34
+A	3 weeks	1153				
+A tb		1021	132	1.61	15	.13
+A	6 weeks	1278				
+A tb		1137	141	1.59	15	.14
+A	Death	1396				
+A tb		1158	238	1.06	15	.306
−A tb	Onset	1092				
+A tb		1096	4	.09	18	> .9
−A tb	3 weeks	1033				
+A tb		1021	12	.17	18	.86
−A tb	6 weeks	1021				
+A tb		1137	125	.63	18	.53
−A tb	Death	990				
+A tb		1158	168	2.01	18	.052

−A = animals on basal diet (vitamin A deficient).

+A = animals on basal diet + 5 per cent butter fat.

tb = infected intravenously with .000,5 mgm. of strain C3.

P = statistic; usually significant when less than .05.

The values t and n have been explained in detail in our first paper under "Statistical method," *Amer. Rev. Tuberc.*, 1936, *33*, p. 588.

weight mean significantly less than that of animals receiving this factor at 3 and 6 weeks on their respective rations. Both groups were killed at the end of the experimental period of 61 days (table 4). One animal on the basal diet showed xerophthalmia. No metaplasia of the epithelium of the trachea was noted on histological examination.

Group 4: Tuberculous animals: Ten rabbits were placed on the deficient ration and 10 on the diet containing vitamin A. They were then inoculated intravenously with .000,5 mgm. of C3, a bovine strain of tubercle bacillus.

TABLE 5

Autopsy findings in rabbits inoculated with .000,5 mgm. of the C3 strain of tubercle bacilli

ANIMAL NUMBER	LUNG	LIVER	SPLEEN	KIDNEY	GROSS TB. SCORE	SURVIVAL
Experimental						
a1	4+*	2+*	3+*	1+*	4+	61
a2	4+*	1+*	1+	1+*	3+	62
a3	4+*	2+*	3+*	2+	4+	61
a4	4+*	0	0	1+*	3+	45D
a5	3+*	0	1+*	0	3+	45D
a6	4+*	1+*	4+*	1+*	4+	58D
a7	4+*	2+	4+	2+	4+	62
a8	3+*	2+*	2+*	1+*	4+	61
a9	4+*	0	3+*	0	3+	50D
a10	3+*	2+	2+*	0	4+	43D
Control						
a21	2+*	1+*	1+*	0	3	54D
a22	4+*	0	2+*	2+	3	61
a23	3+*	2+*	2+	1+	4+	61
a24	1+	0	2+	0	1+	46
a25	3+	1+*	2+	–	4+	46
a26	2+*	1+*	1+*	0	3+	42D
a27	2+*	0	1+*	–	2+	62
a28	4+*	2+	2+*	1+*	4+	62
a29	4+*	2+*	2+*	1+	4+	60
a30	2+*	0	2+*	2+*	2+	62

* Tubercle bacilli found; D = died, others killed. Animals 11–13 uninoculated experimental group, negative for tuberculosis as well as animals 14–20, uninoculated controls.

Pathology: (a) Weights and survival period: Tuberculous rabbits on the diet deficient in vitamin A lost significantly more weight than those on the control diet. As some of the control rabbits were killed when the deficient animals died and all surviving were killed at 61 days, the survival period could not be calculated. Five of 10 tuberculous animals on

the vitamin-A depleted ration died before the end of the experiment. Infected animals on the diet deficient in vitamin A lost significantly more weight than tuberculous control rabbits. There was likewise a significant weight difference at 3 and 6 weeks between uninfected animals depleted of vitamin A and those on the supplemented ration. The weight difference between infected and uninfected vitamin-A deficient rabbits or between infected and uninfected control animals was not significant (table 4).

(*b*) *The deficiency:* Two animals (a4 and a6) developed very definite xerophthalmia and one (a9) had an early stage of this condition when it died of coccidiosis. This did not occur in rabbits receiving vitamin A.

(*c*) *Secondary infections:* Secondary pneumonias were not present in deficient or control animals. It should be recalled that the experiment was terminated at 61 days. Over 50 per cent of the animals died before they were on the diets 6 weeks, usually from a sudden diarrhoea which was caused by coccidiosis in most instances. Only those animals who lived longer than 6 weeks were included in our data.

(*d*) *Tuberculosis:* In the group on the diet producing xerophthalmia, all 10 rabbits developed very advanced tuberculosis, while 7 of 10 control animals had tuberculosis of similar severity. All of the depleted animals had extensive caseous pneumonia; this occurred in only 5 out of 10 rabbits on the supplemented ration. None of the latter animals had lesions of 3 plus or greater severity in the spleen, but 5 of 10 animals in the condition of avitaminosis had tuberculosis of this extent. Tuberculous involvement of the kidney, liver and bone marrow was about the same in both groups (table 5). Intestinal sections showed no tuberculosis.

DISCUSSION

Guinea pigs on a diet deficient in vitamin A showed metaplasia of the normal columnar epithelium to the squamous type as described by Wolbach and Howe (1928) (7). They frequently developed dilatation of the ureters and pelves; in some cases hydronephrosis and small white calculi were found. This condition was first described by Osborne and Mendel in rats (1917) (14). The presence of respiratory infections in vitamin-A depleted animals has been described by numerous investigators (see reviews by Clausen, 1934 (15) and Robertson, 1934 (16)). We found secondary pneumonias to be prevalent in the guinea pigs on the ration deficient in this factor. The animals not receiving vitamin A had

a mean weight and survival period significantly less than those on the basal diet supplemented with the vitamin. However, it is important to note that although these control animals received a diet theoretically adequate in nutritional requirements they had weights definitely lower than those of guinea pigs on a normal diet for this species and few looked as well. Herbivorous animals are accustomed to a large amount of roughage, usually in the form of hay, and this factor is apparently very important in maintaining a condition of physical well-being and maximum growth.

Tuberculous guinea pigs on the vitamin-A deficiency did not die sooner than animals on the deficiency alone nor did they weigh less. Apparently, the added burden of the infection could not further reduce the poor physical condition of the animals caused by the vitamin deficiency. The deficiency evidently caused the death of many of the tuberculous guinea pigs.

The incidence of generalized tuberculosis developing during the experiment was about 50 per cent in the animals not receiving the vitamin and also in those whose basal diet was supplemented with this factor. Although the survival period of the vitamin-A deficient animals was significantly shorter than those on the control diet, an analysis of the animals dying earlier in the experiment, that is, 60 to 80 days, did not show any greater incidence of advanced tuberculosis in the former group of animals. It was, therefore, felt that the tuberculous process was not accelerated in the deficient animals.

When the tuberculosis in the guinea pigs receiving the basal diet supplemented with vitamin A was compared to that in the group of similarly infected animals fed on a normal ration for guinea pigs, the incidence of advanced tuberculosis was much greater in the former group of animals. The unnatural physical form of the experimental diet, although adequate in all the known nutritional factors, apparently lowered the resistance of the animals to some extent. The absence of sufficient roughage in the experimental diet may also account for the greater absorption of organisms ingested in this group, as compared to that in the animals on the normal guinea-pig diet, which were fed large amounts of hay.

It was difficult to correlate the findings in this experiment with those obtained in our previous investigation with vitamin C. Our guinea pigs on the vitamin-C deficient diet supplemented with orange juice were maintained in excellent health for a prolonged period. As already mentioned, animals on the vitamin-A depleted diet supplemented with

butter fat were not so maintained. When sputum was fed to animals on the diets just mentioned, those on the diet with vitamin A had more generalized tuberculosis than the vitamin-C control guinea pigs.[4] This was even more striking since the mean survival time of the animals in this experiment was 81 days and that of the guinea pigs on the vitamain-C control ration was 142 days. When infected vitamin-A deficient animals were compared with infected animals on the diet of chronic scurvy, the latter had more generalized tuberculosis. However, the mean survival period of the animals depleted of vitamin A was only 68 days and that of the chronic scorbutic animals was 119 days.

Rabbits were inoculated with a small dose of strain C3 which proved to be very virulent. Extensive advanced tuberculosis developed in a short time and animals were killed as it was feared any difference caused by the vitamin deficiency might be masked. The incidence of advanced tuberculosis appeared to be slightly greater in the animals on the depleted ration. These animals seemed to have a definitely greater involvement in the lungs and spleen but, due to the small number of rabbits surviving long enough to be included in our data, accurate analysis is not possible. With a much larger series and a less virulent strain of tubercle bacilli, it might be possible to establish these findings definitely.

CONCLUSIONS

1. Guinea pigs and rabbits receiving a vitamin-A depleted basal diet supplemented with vitamin A could not be maintained in excellent health as were those receiving their respective normal diets.

2. Vitamin-A deficiency caused a significant lowering in body weight as compared to that of animals on the basal diet with added vitamin A.

3. Vitamin-A depleted guinea pigs survived for a shorter period than animals receiving the vitamin.

4. Pneumonia occurred in a high percentage of guinea pigs depleted of vitamin A.

5. Dilatation and swelling of the ureters with calculus formation were found in some of the guinea pigs on the diet producing avitaminosis.

6. The development of tuberculosis did not appear to be accelerated in vitamin-A deficient guinea pigs, especially those surviving from 60 to 80 days after infection.

7. Tuberculosis did not further reduce the weights nor the survival span of guinea pigs depleted of vitamin A.

[4] Vitamin-C control guinea pigs were animals on scorbutic basal diet plus orange juice.

8. Tuberculous infected guinea pigs on a basal diet supplemented with all the known food factors developed more extensive lesions than similarly infected animals on a normal ration for this animal.

9. Rabbits on a diet deficient in vitamin A appeared to develop slightly more extensive tuberculosis in the lung than control animals, when inoculated intravenously with strain C3.

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THE SEDIMENTATION RATE AND MEDLAR'S INDEX[1,2]

A Comparison

A. R. MASTEN

The blood is a sensitive reflector of alterations occurring anywhere in the body. Throughout life there is a constant interchange taking place between the blood and the other body tissues. This interchange produces continued variations in the composition of the blood both in its liquid and solid constituents. In spite of these constant variations a number of adaptive processes cooperate in maintaining an equilibrium, which in health gives the blood a uniform composition in both its histological structure and its chemical composition. Disease conditions usually destroy this normal equilibrium with the production of definite changes, which, when rightly interpreted, give valuable information regarding the underlying pathology.

For many years efforts have been made to establish a characteristic blood picture which would be helpful in evaluating the underlying pathology in tuberculosis. The establishment of such a picture would, it was thought, be of inestimable value to the clinician since it would enable him to determine with greater accuracy both the extent of the lesion and the course it was pursuing, and at the same time give definite information regarding the effectiveness of treatment. In regard to treatment it was hoped that such a picture would be of great aid in determining the time when any particular type of treatment should be instituted as well as the length of time it should be maintained. These objectives have been attained to a considerable degree by studies of both the corpuscular and plasma content of the blood. To-day important information regarding a tuberculous lesion can be derived from the white blood-picture as exemplified in Medlar's leucocytic index; and from the plasma-corpuscular relationship shown by the red-cell sedimentation rate.

Studies to determine the significance of leucocytic changes occurring

[1] From the Lutheran Sanitarium, Wheat Ridge, Colorado.

[2] Read at a meeting of the Denver Sanatorium Association, Denver, Colorado, May 26, 1936.

in the blood of tuberculous patients began years ago. In 1905 Ullom and Craig (1) came to the conclusion that an increase of resistance to a tuberculous infection was accompanied by a corresponding increase in the number of lymphocytes in the blood. In 1925 Sabin, Cunningham and their coworkers (2) found that the course of a tuberculous lesion could be quite accurately followed by noting the relative proportions of monocytes and lymphocytes in the circulating blood in rabbits. It was found that when the monocyte-lymphocyte ratio was low, that is, when there was an increase in the monocytes, autopsy always disclosed an extensive and active lesion. On the other hand when the lymphocytes showed an increase, that is, when the monocyte-lymphocyte ratio was high, autopsy consistently showed an attenuated or arrested lesion. In 1926 Medlar (3) began an extensive study of the leucocytic reaction in tuberculosis. From his studies he arrived at the conclusion that there are three definite leucocytic types which are produced by tuberculous lesions at different stages of the pathological process. The neutrophiles, he says, predominate in the phase of abscess-formation, of cavitation and of ulceration. The lymphocytes are the chief cells concerned with the healing process, and the monocytes increase when extention of the tuberculous lesion takes place. In 1935 Crawford (4) in conjunction with Medlar, devised a calculator for correlating Medlar's three types of cell reaction into one index number, which he calls the leucocytic index. In this paper this index is referred to as Medlar's index.

The value of the plasma-corpuscular relationship as shown by the red-cell sedimentation rate has been amply demonstrated since 1921 when Westergren (5) first urged the use of this valuable test in tuberculosis. In previous papers (6) (7) we showed that the sedimentation rate is an efficient method of determining the activity and of following the course of tuberculosis. In this paper the sedimentation rate refers to the percentage of fall of the red-cells in a two-hour period as determined by use of the modified Westergren technique described in the aforementioned articles (6) (7).

The present study was made in order to determine a relationship, if any, between the sedimentation rate and Medlar's index. The accuracy of the two tests in reflecting the clinical course of tuberculosis was investigated also, although the number of patients having coincident blood counts and sedimentation tests was found to be rather small for accurate statistical analysis. In spite of this drawback, however, several interesting relationships were discovered and it is hoped that further study will lead to their eventual confirmation.

In 1930 we began making sedimentation tests on all patients entering this institution so that we now have records of 158 consecutive tuberculous patients showing complete blood counts and sedimentation rates, together with a classification into minimal, moderately advanced and far advanced cases as determined by history, physical examination and X-ray. In this series there were 18 minimal, 35 moderately advanced and 105 far advanced patients. These groups showed a definite and parallel increase in their median sedimentation rate and Medlar index as shown in the following:

	Minimal	*Moderately Advanced*	*Far Advanced*
Median sedimentation rate	20	31	44
Median Medlar index	23	26	36

There is a definite correlation between the two tests, a high sedimentation rate and a high Medlar index closely paralleling extensive disease. Conversely a low sedimentation rate and a low Medlar index accompany a slight lesion.

The 158 patients were next grouped according to their progress in the sanatorium, that is, into those who improved, those who remained stationary or grew worse, and those who died. The number of patients in each of these groups was 111, 27 and 20 respectively.

	Improved	*Stationary and Worse*	*Died*
Median sedimentation rate	34	38	47
Median Medlar index	32	36	41

From these findings it appears that both tests have a definite relationship with the extent of the disease, for it is well known that the smaller amount of tuberculous involvement when treatment is started the greater is the probability of cure. Likewise it is evident that the lower the sedimentation rate and Medlar index the greater are the chances for improvement. Conversely the higher the sedimentation rate and Medlar index the worse is the prognosis.

The change which occurs in the sedimentation rate and Medlar index during the course of tuberculosis was studied in 65 far-advanced patients who had blood counts and sedimentation tests made concurrently several times during their stay in the sanatorium. It was found that in 77 per cent of these patients the sedimentation rate followed the clinical course of the disease. Medlar's index followed the clinical course in 58 per cent of the same patients. In 57 per cent of the patients the sedimentation rate and Medlar's index followed the clinical

course in unison. Although in this group the sedimentation rate followed the clinical course more accurately than did Medlar's index, individual cases frequently showed the opposite to be true. For example, a patient who developed acute appendicitis showed a marked rise of Medlar's index while the sedimentation rate remained essentially unchanged. Medlar's index appeared to reflect the severity of the intercurrent infection while the sedimentation rate continued to parallel the underlying tuberculosis. This is to be expected since Medlar's index is largely influenced by the neutrophile-lymphocyte ratio, while the sedimentation rate depends upon tissue destruction.

In the group of patients having concurrent sedimentation tests and blood counts several times during their course of treatment 48 showed definite clinical change as confirmed by X-ray findings. Thirty-one of these patients improved and 17 grew worse. A comparison between their median sedimentation rate and Medlar index at entrance and their last examination showed a fall of both the sedimentation rate and Medlar index in those patients who improved and a rise in those who grew worse. This relationship is well shown in the following tabulation:

		Improved	*Grew Worse*
Median sedimentation rate	Entrance	40	32
	End of observation	21	42
Median Medlar index	Entrance	32	33
	End of observation	29	47

From the above it is seen that there is a definite and parallel fall shown by both the sedimentation rate and Medlar's index in those patients who improved; and a positive increase of both tests in those patients who grew worse.

SUMMARY

From this study it appears that both the sedimentation rate and Medlar's index indicate the activity of a tuberculous lesion, and that both tests follow the course of the lesion quite accurately. Thus the higher the sedimentation rate and Medlar index the worse the prognosis; conversely the lower the sedimentation rate and Medlar index the better the prognosis. Because of variations in individual instances it would seem that both tests are well worth while and should be made to supplement each other. Where conditions prohibit the employment of both procedures the simplicity of the red-cell sedimentation test is an important point in its favor.

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PRECIPITATION OF WATER SOLUBLE TUBERCULOPROTEIN BY HYDROGEN-ION CONCENTRATION[1]

ERNEST B. HANAN AND WALTER P. ERICKS

In attempts to develop a procedure for precipitation of tuberculin-like substances from the urine of patients with active tuberculosis the authors employed the buffer solution method of hydrogen-ion concentration. Working with known solutions of tuberculoprotein, it was observed that the optimum pH concentration for maximum precipitation was approximately 2.8. This is apparently in disagreement with the results obtained by both Gabbe (1) and Long and Seibert (2). These investigators placed the isoelectric point for maximum precipitation at approximately pH 4.0.

In view of the importance of this observation in relationship to the chemistry of tuberculosis it was deemed advisable to investigate this point more thoroughly.

PROCEDURE

Various buffer solutions were tried with different preparations and amounts of tuberculoproteins. The experiments presented here were performed with the standard buffer solutions of Clark and Lubs (3). A series of 30 different pH concentrations ranging from 1.2 to 7.0 was tested. These pH concentrations were measured before and after the addition of the protein solutions by the colorimetric method and checked by the potentiometer. Care was used not to disturb the pH equilibrium of the buffer solutions by addition of too much protein extract.

The tuberculoprotein solutions tested were the ultraprotein filtrate prepared according to the method of Seibert (4); distilled water extracts of virulent and avirulent tubercle bacilli; and the undialyzed culture filtrate of avirulent tubercle bacilli grown on Long's (5) nonprotein media.

In the experiments described in this communication, the undialyzed culture filtrate was used. It was found that 0.5 cc. of the filtrate could

[1] From the Laboratories of the Buffalo City Hospital and Medical School, University of Buffalo, Buffalo, New York.

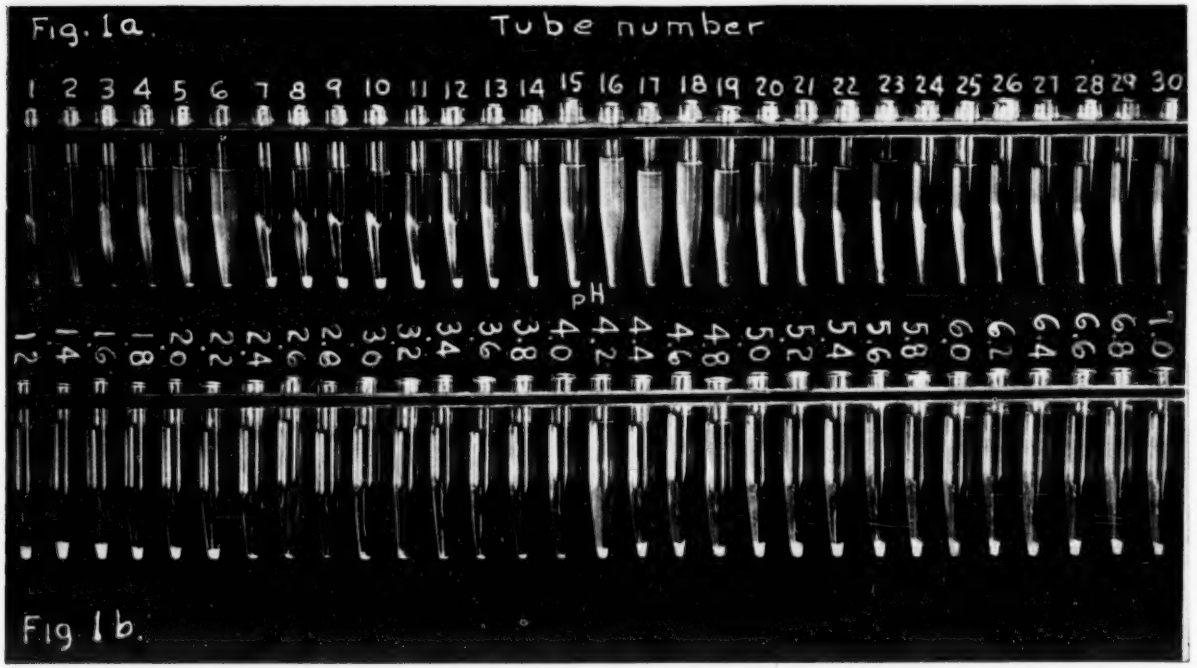

FIG. 1a. Showing the precipitation of unheated tuberculoprotein by hydrogen-ion concentration using Clark and Lubs's buffer solutions. The pH range is from 1.2 to 7.0. Optimum pH for maximum precipitation is 2.8 with a range from 2.4 to 3.0.

FIG. 1b. Showing precipitation of the tuberculoprotein from supernatant fluids of test shown in fig. 1a using 10 per cent concentration of trichloroacetic acid. Note that practically no precipitate appears at pH 2.8.

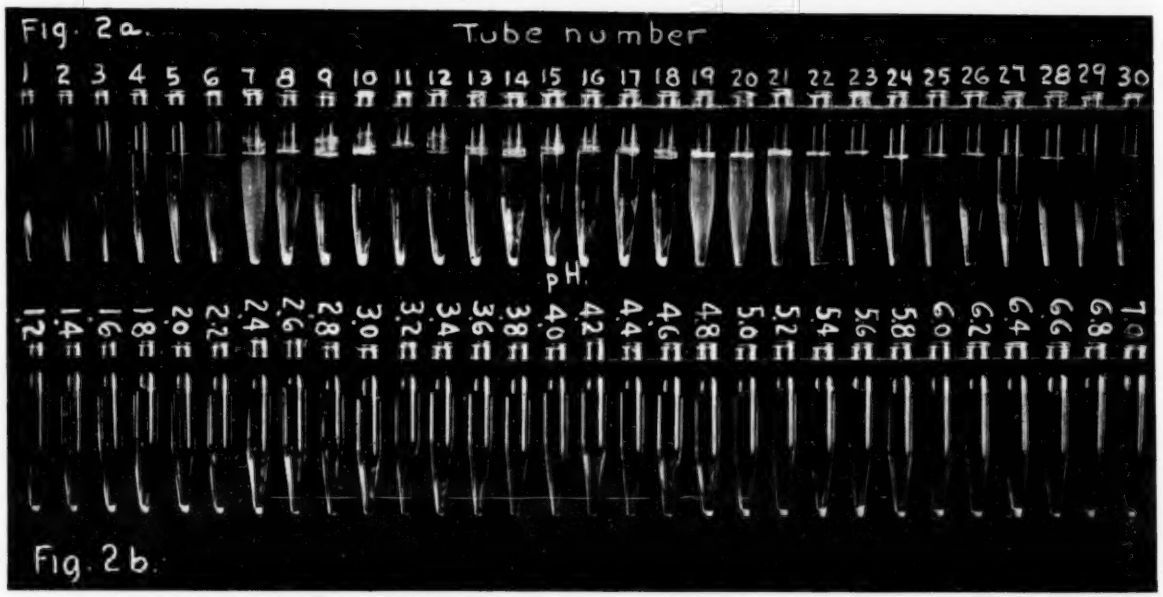

FIG. 2a. Showing pH precipitation of heated tuberculoprotein using the same technique as in fig. 1a. Note that the range of maximum precipitation shifts to the alkaline side to pH 4.6.

FIG. 2b. Trichloroacetic acid precipitation of supernatant fluids of experiment 2a. Note that practically no precipitate appears within the pH range of maximum precipitation.

be added to 9 cc. of the buffer solutions without disturbing the pH equilibrium. Nine cc. of each buffer solution was pipetted into a centrifuge tube followed by 0.5 cc. of the culture filtrate. This was mixed and observed for the appearance of flocculation; then, after standing overnight, the tubes were centrifuged and observed for the pH concentration of maximum precipitation.

The supernatant fluids were then transferred to another set of tubes and tested by various protein precipitants for completeness of precipitation. In these experiments, trichloroacetic acid was added making a 10 per cent concentration, and after standing overnight the tubes were centrifuged. The completed experiment is shown in figures 1a and 1b.

Following this a culture filtrate was boiled for one hour and the experiment repeated as shown in figures 2a and 2b.

RESULTS

In the experiments with the different tuberculoprotein solutions, it was observed that flocculation appeared first at pH 2.8. This was the finding regardless of the method of preparation of the protein solution. On standing overnight the maximum range for the unheated culture filtrate extended from pH 2.4 to 3.0 as shown in figure 1a and also tended to extend toward the alkaline side to pH 4.0 but precipitation was not complete beyond pH 3.0.

With the heated culture filtrate, the flocculation appeared first at pH 2.8 but on standing overnight the maximum range of precipitation extended toward the alkaline side to pH 4.6 as shown in figure 2a.

When tricholoracetic acid was added to the supernatant fluids as shown in figures 1b and 2b, very little precipitate occurred within the maximum range of pH precipitation.

DISCUSSION

Our experience with the pH precipitation of tuberculoprotein has shown that with the undenatured material the optimum point for the maximum precipitation is approximately pH 2.8 with a range between 2.4 and 3.0. However, when subjected to hydrolysis as in heating, the maximum range extends towards the alkaline side to as high as pH 4.6. This was especially noted with the distilled aqueous heat extracts of tubercle bacilli.

Attempts were made to repeat the experiments of Long and Seibert,

using acetic acid. A series of 60 tubes were set up, each containing 9 cc. of a diluted aqueous extract of avirulent tubercle bacilli.

Beginning with dilute acetic acid that gave no precipitate in the first few tubes, the amount of acid was increased in each successive tube until no precipitate occurred in the last few tubes. The pH was determined colorimetrically in the supernatant fluid of each tube. It was found that the pH did not consistently vary in proportion to the amount of acid but it was interesting to note that all maximum precipitations occurred within the pH 2.4 to 4.6 range. This was the same range as obtained with the same extract using the buffer solutions.

Blood serum or egg albumen (using the same buffer solutions) does not precipitate at pH 2.8. This would indicate that tuberculoprotein is probably not albuminous in nature as has been suggested by some investigators (6) (7). At least it does not precipitate in the albumen pH range until subjected to hydrolysis. This may have caused confusion since the hydrolyzed material has probably become a mixture of derived proteins, some of them albuminous in nature.

The precipitate obtained at pH 2.8 is readily soluble in distilled water made slightly alkaline with sodium-bicarbonate. It gives positive biuret and xanthoproteic reactions and contains a carbohydrate radical as indicated by Molisch's test.

Its antigenic properties were demonstrated by the characteristic tuberculin skin reactions on tuberculin-sensitive individuals. A satisfactory antigen for complement fixation tests has been prepared in our laboratory by using a precipitate obtained by adjusting the aqueous extract of tubercle bacilli to pH 2.8 with glacial acetic acid.

There are but few proteins that precipitate at so low a pH. This suggested a chemical aid for isolation and purification of tuberculoprotein. In order to test this possibility, a mixture of tuberculoprotein and human serum in equal amounts was added to a series of buffer solutions, and allowed to stand overnight. At the lowest pH of maximum precipitation (pH 2.4) very little serum proteins were adsorbed to be carried down by the tuberculoprotein, but as the alkaline side was approached more and more serum proteins were carried down. In the pH range for precipitation of serum proteins the tuberculoproteins were apparently adsorbed and carried down with the serum proteins.

This reaction has not been investigated further at the present time. However, we have used the pH 2.8 precipitation as an aid in the isolation

and purification of the tuberculin-like substances in the urine of patients with active tuberculosis with some degree of success.

The authors feel that on further studies this low pH flocculation point may prove to have considerable bearing upon our knowledge concerning the nature of the disease processes of tuberculosis. It may also explain some of the difficulties encountered in laboratory procedures now employed as aids in diagnosis of the disease.

SUMMARY

1. By use of buffer solutions it was found that with undenatured tuberculoprotein the maximum precipitation occurs at approximately pH 2.8 with a range from 2.4 to 3.0.

2. When tuberculoprotein is subjected to hydrolysis the range of maximum precipitation shifts toward the alkaline side to as high as pH 4.6.

3. It is suggested that this low pH 2.8 precipitation point may serve as a chemical aid in the isolation and purification of the tuberculoprotein.

4. It is further suggested that continued studies of pH precipitation characteristic of tuberculoprotein may have an important bearing on our knowledge concerning tuberculosis.

The authors wish to express their appreciation to Alexander Terech and William Millerschoen for their invaluable technical assistance rendered in these studies.

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TOPICAL APPLICATION OF CODLIVER OIL IN TUBERCULOSIS[1]

A Preliminary Report

ANDREW L. BANYAI

The administration of codliver oil by mouth was known for a long time before experimental evidence was produced that demonstrated its possible mode of action. In the earliest references its alleged usefulness was attributed to its relatively easy absorbability from the intestinal tract and to its high caloric value.

When it became known that codliver oil contains large amounts of vitamin A and vitamin D, it was demonstrated that certain healing properties of it were due to these vitamins.

The results observed by Loehr (1) following the local application of codliver oil in nontuberculous conditions are of interest. He used codliver oil and a codliver-oil salve for the treatment of fresh wounds, burns, acute and chronic osteomyelitis. He noted that codliver oil exerts a striking inhibiting effect upon the bacterial flora of wounds. The oil permeates the tissues and causes a rapid liquefaction of the necrotic tissues, including the epithelium. There is an early appearance of granulation tissue which, in turn, becomes covered with epithelium. The most striking regenerative effect on the epithelium was seen in burns.

The favorable effect of codliver oil upon the formation of granulation tissue was observed by Steel (2) in the treatment of deep abrasions, burns, and indolent ulcers in the leg.

Loehr (1) emphasizes the fact that bacteria ordinarily encountered in infected wounds, such as streptococci, staphylococci and *Bacillus coli*, perish when introduced into codliver oil. It has not been determined whether the microörganisms die because the codliver oil contains no nourishment for them or because of the surface tension of the oil. He believes that the beneficial effect of codliver oil upon the healing of wounds is attributable to its vitamin A and D content.

[1] From the Muirdale Sanatorium, Wauwatosa, Wisconsin.

Fontes (3) reported in 1921 that the addition of one per cent codliver oil to ordinary broth medium prevents the development of cultures of tubercle bacilli. The oil in the fluid medium did not lose this inhibiting power when filtered through porcelain but did lose it when shaken with kaolin. Fontes assumed that the bacilli absorb particles of oil which forms an insulating envelope that, in turn, obstructs the nutrition and oxygen supply of the microörganisms.

The inhibitory effect of codliver oil upon the growth of tubercle bacilli was believed by Platonov (4) to be due to unsaturated fatty acids. He added the unsaturated soaps of codliver oil to cultures of tubercle bacilli on potato media. After three weeks it was found that unsaturated soaps, even in concentration of 0.25 per cent, inhibit the growth of the bacilli. When suspension of tubercle bacilli in a one or two per cent solution of unsaturated soaps was used, the effect was still greater. After 48 hours in the incubator, the preparation stained by the Ziehl-Neelsen method had an interesting appearance: the tubercle bacilli were pale pink, contained dark granules and a considerable number of them had lost their acid-fastness.

A similar investigation was carried out by Campbell and Kiefer (5). They cultured tubercle bacilli on codliver-oil-potato medium. After five weeks the tubercle bacilli appeared beaded and smaller than the usual size. Some of them had a dumb-bell shape and seemed to be composed of two granules united by a very thin short strand of red-staining protoplasm. With the granule stain, the red-staining protoplasm was not very evident. Many solitary granules were seen. They concluded from their investigation that codliver oil has a definite inhibitory and bactericidal action on virulent tubercle bacilli. From the study of controls on cotton-seed oil they deduced that at least part of the inhibitory action is caused by some constituent of the codliver oil and not altogether by a mechanical action of a film of oil between the bacterium and the medium.

Loehr (1) also reported that codliver oil is free of bacteria and, even when used in large quantities locally, it is harmless.

This paper is based upon the observation of 46 cases. Of these there were 3 lupus vulgaris, 1 scrofuloderma, 1 case with multiple subcutaneous tuberculous abscesses, 6 with tuberculous lymphadenitis, 1 so-called primary tuberculosis of the muscle, 2 tuberculous ulcers of the pharynx, 25 with tuberculous laryngitis, 3 with tuberculous empyema, 1 sinus following tuberculous epididymitis, and 3 ischiorectal fistula

cases. Patients whose treatment lasted for less than two months were not included in this study.

Of the 3 lupus vulgaris cases, 2 completely recovered in eight and four months, respectively; the third patient whose lesion involved the middle and upper portions of the left arm has shown remarkable improvement during the five months from the beginning of treatment on March 2, 1936. This patient, N. Z. (no. 8348), 33 years old, white, female, has been suffering from skin tuberculosis for approximately twenty years. Although the lesion showed considerable improvement on a modified "salt-free" diet, rather large, persistently discharging ulcerous areas were still present at the beginning of codliver-oil treatment. As an illustration of complete healing the following case is presented.

O. K., (no. 6814), 27 years old, white, female. Diagnosis: Lupus vulgaris, involving practically the entire face, with partial destruction of the nose and upper lip. Also, lupus vulgaris, involving the entire extent of the skin of the left arm. The disease was of 6 years' duration when patient was first seen. The process responded favorably to "salt-free" diet, but some of the ulcers on the face and arm remained open and produced considerable discharge. Codliver-oil dressings were applied to these areas from October 4, 1934 until May 31, 1935, at which time all ulcers were found to be epithelized. The favorable change in the process of healing was so marked following the local application of codliver oil, that it seems to be justified to attribute the acceleration and completion of the healing to the effect of codliver oil.

Favorable response to treatment is present in a case of scrofuloderma following a period of treatment of $4\frac{1}{2}$ months. The process is not entirely healed yet. The lesion in this patient, M. C. (no. 7856), 13 years old, Mexican, male, developed at the site of multiple sinuses originating from tuberculosis of the right 6th rib.

Slow but satisfactory improvement followed the application of codliver oil to ruptured tuberculous subcutaneous abscesses. This child, W. F. (no. 9384), 15 years old, colored boy, was suffering also from multiple bone tuberculosis and tuberculous lymphadenitis.

Very good results were observed in all the six cases of tuberculous adenitis. Two cases are presented in detail.

1: A. B., (no. 10197), 2 years old, white, female. Diagnosis: tuberculous lymphadenitis, preauricular. On admission there was a fluctuating mass the size of a large walnut anterior to and below the right ear. The skin over

this abscess was markedly congested and atrophic. The patient was treated by daily quartz-lamp irradiations at the Milwaukee Children's Hospital prior to her registration at the sanatorium, without improvement. Fifteen cc. of pus were removed from the abscess by aspiration, following which 5 cc. of warm codliver oil were injected into the abscess on April 4, 1936. The abscess broke through the skin two days later. Next day it closed up again and began to fill up. Four cc. of pus were aspirated and 2 cc. of warm codliver oil injected on April 11, 1936. The abscess opened spontaneously the same night. From then on the local treatment consisted of daily instillations of codliver oil by means of medicine dropper and of the application of codliver-oil dressings over the discharging sinus. The discharge gradually diminished and complete healing ensued in three months.

The development of a small fluctuating abscess, originating from a tuberculous lymphadenitis was noted under the chin on April 25, 1936. Aspiration was unsuccessful. When this abscess opened spontaneously, codliver-oil dressings were applied locally. On July 25, 1936 there were two small sinuses under the chin. The drainage from them was only occasional and scanty. Codliver-oil dressings were substituted by the topical application of an ointment that consists of equal parts of codliver oil and vaselin.

2: M. P., (no. 10079), 15 years old, white, male. Diagnosis: bilateral tuberculous inguinal adenitis. Two months prior to his admission to the sanatorium he noticed a progressive swelling in both inguinal areas, about the size of small eggs. Two weeks later both swellings were surgically evacuated at the Milwaukee County General Hospital. The diagnosis of tuberculosis was confirmed by a postoperative biopsy. Both wounds measured about 9 cm. in length and had a profuse, purulent discharge when first seen. Codliver-oil packs were applied twice daily. Three weeks after the beginning of this treatment a walnut-sized swelling developed above the left incision. It disappeared in about a week without surgical intervention. After six weeks' treatment with codliver oil the right wound was completely filled with granulation tissue and was partly covered with new epithelium; the healing of the left side was somewhat slower, but the granulation and epithelization were progressing satisfactorily. No other local measures were applied. The patient gained 8.5 kgm. (19 lbs.) in seven weeks and 12.5 kgm. (27.5 lbs.) in 8 months. Complete healing occurred in 8 months.

The case of a so-called primary tuberculosis of the muscle is presented briefly.

R. W., (no. 9570), 40 years old, white, male. Diagnosis: (1) Far-advanced pulmonary tuberculosis; (2) so-called primary tuberculosis of the muscle,

left forearm. The tuberculous mass was removed surgically by Dr. F. Raine on October 12, 1935. Because of the persistent drainage following this operation, codliver-oil packings were applied daily from November 29, 1935. There was a rapid diminution in the amount of discharge shortly after beginning of this treatment. The wound healed completely and was well epithelized in six weeks.

The rapidity with which tuberculous pharyngeal lesions cleared up was surprising. The following case illustrates this point.

L.L., (no. 10103), 20 years old, white, female. Diagnosis: (1) Far-advanced pulmonary tuberculosis; (2) tuberculosis of the tonsils and peritonsillar structures; (3) tuberculous laryngitis. The patient stated that her throat condition developed two months before her admission to the sanatorium. She complained of sore throat and dysphagia. Both anterior and posterior pillars and both tonsils were markedly congested; the right tonsil and the right anterior pillar were definitely ulcerated. The same involvement was present on the left side, although not very extensive. There was considerable anterior cervical adenopathy. The throat was cleansed with Dobell's solution, and codliver-oil spray was applied locally three times a day. In three weeks the ulcers disappeared, the margins of the pillars were smooth, and congestion of these structures entirely cleared, except the posterior part of the right tonsillar fossa; the latter was found normal 4 weeks later. The soreness of the throat and dysphagia disappeared.

It is interesting to note that her larynx has shown a healing of the tuberculous ulcers but the oedema persisted, although it was treated with codliver oil during the same period.

All patients in the laryngeal tuberculosis group had an active pulmonary tuberculosis. Some had also other extrapulmonary complications. As to the pathology, a great many manifestations of the disease were seen, from a well circumscribed infiltration to ulceration, marked interarytenoid vegetative granulation, and extensive oedema.

The treatment of the larynx consisted of spraying it with codliver oil by means of an atomizer three times a day. The spray was given always after meals for avoiding possible anorexia caused by the taste of the oil. The oil must be warmed prior to its application, for two reasons: (1) heating diminishes its viscosity, and (2) the diseased mucous membrane tolerates warm oil better than cold oil. The patient is instructed to hold the tongue between the thumb and the index

finger. Pulling the tongue forward with moderate force causes a rise of the larynx and thereby facilitates the proper focusing of the spray. The nurse or attendant, instructed in the technique, holds the downward directed tip of the atomizer slightly beyond the root of the tongue, without touching the pharyngeal structures. The patient breathes in and out somewhat faster than usual; 10 to 12 compressions of the bulb of the atomizer deliver a sufficient amount of oil into the accessible parts of the larynx.

The length of treatment varied from 2 to 6½ months.

The evaluation of the effect of codliver oil in laryngeal tuberculosis is rather difficult for several reasons. Tuberculous laryngitis may show a spontaneous healing in its early stages. Its course may parallel that of the pulmonary process. When the general condition of the patient, his immunity and defense are poor the chances for improvement in a serious laryngeal tuberculosis are very slight.

Still it seems that, perhaps, with the exception of cases with marked laryngeal oedema, or when the pulmonary tuberculosis is very advanced, it is worth while to resort to codliver-oil treatment. The restoration of normal voice, the elimination of dysphagia, the relief from soreness in the larynx and from exhausting cough, improved expectoration, and restoration of normal sleep, that accompanied objective evidence of improvement in some of our cases, speak very much in favor of such an attitude.

Of the 25 patients in this group, 17 improved and 8 did not. Of the 8 patients who showed no improvement 6 had far-advanced pulmonary tuberculosis. Some of them have serious complications, such as, diabetes, empyema, and renal tuberculosis. Marked laryngeal oedema was present in four. This type of lesion is particularly resistant to local treatment. Of the 17 patients who improved, 9 had far-advanced pulmonary processes.

Three cases of tuberculous empyema were treated. The treatment consisted of the injections of 45 to 300 cc. of codliver oil into the thoracic cavity through a catheter that had been inserted previously. None of these patients showed a satisfactory improvement on surgical drainage following costectomy. The treatment was well tolerated by the patients. No local or general reactions resulting from the treatment were observed. One patient, R. W., (no. 9658), white, male, who had a progressive pulmonary tuberculosis on the "good" side, died. The

treatments were given for 2½ months. A slow but definite improvement has been noticed in the second case, N. S., (no. 9757), 34 years old, white, male. The details of the course of treatment in the third case were as follows:

S. J., (no. 4192), 37 years old, colored, male, was discharged from the sanatorium as an apparently arrested case of far-advanced pulmonary tuberculosis on October 22, 1934. At the time of his readmission, July 2, 1935, he complained of loss of weight and strength, and stated that he noticed a swelling over the right breast region. The right thoracic cavity was aspirated on several occasions and pus removed. An *empyema necessitatis* developed on July 23, 1935. There was a persistent purulent drainage through the sinus. The temperature that rose over 39°C. shortly after his admission, returned to normal in four months, with occasional subfebrile rises. A costectomy was performed and drainage established on November 14, 1935.

Because of the persistent drainage and because of the lack of improvement in the patient's general condition we resorted to the injection of about 150 cc. of codliver oil into the empyema cavity on February 25, 1936. Following the injection the drainage tube was clamped near the chest wall, and the clamp was left in place from half an hour to two hours; then drainage was established through a tube, the distal end of which was connected to an ordinary drainage bottle. The oil was warmed to body temperature prior to the injection. These treatments have been repeated once a day. No pleural reaction, pain, discomfort or cough followed the injections. The amount of purulent discharge became gradually less, and it was found to be thinner and more watery than before as the treatment progressed.

The patient is in a greatly improved general condition. He gained 13.5 kgm. (29.7 lbs.) in weight in 5 months, since the beginning of the codliver-oil treatment.

A gradual improvement has been observed in a patient with a tuberculous fistula following an operation for tuberculous epididymitis. The duration of treatment is six months. Recently, because of the shallowness of the sinus tract, the codliver oil, that was applied by means of a medicine dropper directly into the sinus previously, was substituted by a 50 per cent codliver-oil ointment.

Patients with ischiorectal fistulae were given daily injections into the fistula after cleansing it with physiological saline solution. Warm oil is more likely to penetrate the fistulous tract than cold oil. There was marked improvement in 2 and complete healing in 1 patient. In the latter case recovery occurred in 5 months.

J. K., (no. 6494), 33 years old, white, male. Diagnosis: (1) Far-advanced pulmonary tuberculosis; (2) tuberculous laryngitis; (3) tuberculous ischiorectal fistula. The rectal fistula was of three years' duration when local treatments were started with daily injections of codliver oil. After six weeks' treatment the pain, that prior to treatment was radiating upward along the spine, became less marked, the amount of discharge markedly diminished, and the sinus tract, that previously admitted the tip of a rather large syringe, was so well filled with granulation that only a medicine dropper could be used for injecting the oil. Complete healing in 5 months.

W. C., (no. 8920), 19 years old, white, male. Diagnosis: Active far-advanced pulmonary tuberculosis. Complications: (1) Tuberculous laryngitis; (2) tuberculous ischiorectal fistula. A draining ischiorectal fistula was noted on August 11, 1935. A second fistula developed on November 11, 1935. Treatment with codliver-oil injections into the fistulous tracts began on December 15, 1935. The injections were given with the patient in the prone position. He was kept in this position for 20 minutes after each injection. The treatments have been repeated daily. The patient reported subjective improvement in the rectal condition on January 9, 1936. On periodic examinations it was found that the amount of discharge was decreasing. The amount of codliver oil that we were able to inject was getting less also. On April 30, 1936 the lower fistulous tract was found to be noticeably decreased in depth; its cutaneous opening showed a clean granulation tissue, and only a shallow crater remained from the deep tract. The lateral sinus healed entirely. The patient's general and pulmonary condition remain stationary.

SUMMARY

Because of the limited number of cases, no attempt is made to draw definite conclusions. It may be stated, however, that codliver oil can be applied topically with safety in tuberculous laryngitis and pharyngitis, ischiorectal fistulae, lupus vulgaris, suppurating tuberculous lymphadenitis, tuberculous empyema, and other forms of tuberculosis described above.

The favorable results seen in certain types of tuberculosis in our cases invite further study of the therapeutic value of the topical application of codliver oil.

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PARACARDIAC PULMONARY EMPHYSEMA[1]

A Heretofore Undescribed X-ray Shadow Complex

EPHRAIM KOROL[2]

In many chest roentgenograms a group of curvilinear shadows is seen running parallel to the left border of the heart, about one centimetre outside of it. The space between this crescent-shaped density and the heart is very transparent, producing a halo effect about the left border of the heart. The halo may be followed through the shadow of the dome of the diaphragm to the lower border of the lung (figure 1). Upon closer inspection this bright area is seen to be crossed by several fine curved lines which outline circular and oval areas of transparent lung. In many cases a similar region of transparent lung with a dense outer border is seen to the left of the descending aortic arch. Less often the lung in the vicinity of the right border of the heart shows similar changes. Upon stereoscopic examination it can be seen that the lung changes are situated in the front of the chest near the anterior chest wall, while bronchographic examination shows that the shadows are not related to the bronchial trunks (figures 4a and 4b).

The transparent lung areas become more conspicuous on films taken in expiration; the transparencies are accentuated in contrast with the opacification of the lung bases occurring in expiration. Apparently we are dealing with lung tissue which does not deflate well during expiration, that is, with emphysematous lung.

We have had the opportunity to follow three cases with these paracardiac lung changes to postmortem examination; in all cases there was pronounced emphysema in the left upper lobe, chiefly involving the lingula, and there were no other changes such as bronchiectasis, tuberculosis, etc., to account for the roentgen shadow complex.

The paracardiac emphysema when developed sufficiently to show on the X-ray film is generally associated with an enlarged heart. In its most pronounced degree it occurs in cases of aortic regurgitation. We

[1] Published with the permission of the Medical Director of the Veterans Administration, who is not responsible for opinions expressed or conclusions drawn by the author.

[2] Veterans Administration Facility, Lincoln, Nebraska.

have not observed this shadow complex in cases of small centrally-placed hearts. In these cases the descending vascular trunks come to show outside of the heart shadow, but the transparent area of lung tissue described above does not appear in these cases.

It should be emphasized that this shadow complex is not evidence of generalized emphysema. In fact it is seldom seen in severe bullous emphysema and in the forms of obstructive emphysema associated with asthma and chronic bronchitis. Rather, the shadow complex is an expression of emphysematous changes affecting the lobules immediately adjacent to the heart and aorta. The causes of this emphysema reside in the traumatizing action which the pulsating heart has on the surrounding lung.

Fig. 1. Aortic regurgitation of twenty years' duration. The heart action was very forcible and fluoroscopically there was striking overactivity of the left ventricle and of the aorta. The pulse-pressure was 120: systolic 160, diastolic 40 mm. Hg. The base of the left lung is more transparent than the right and the diaphragm is depressed on this side. Outside of the heart border there is the typical crescent of paracardiac emphysema. A similar band of emphysema borders the descending aorta.

Fig. 2. Case of hypertensive heart disease. Blood-pressure 200/120 mm. Hg. The apex impulse was heaving in character and there was a cardiorespiratory murmur. The left base is emphysematous, the transparent lung overlapping the heart apex and the dome of the diaphragm. Note the crescents of paracardiac and preaortic emphysema.

Fig. 3. Double mitral lesion of many years' duration. The crescent of paracardiac emphysema is well marked. In this figure the border of the emphysema crescent is fortified with pencil marks.

Fig. 4a. Case of hyperthyroidism. Increased rate and force of heart. Blood-pressure 150/80 mm. Hg. Cardiorespiratory murmur. Note the ribbon of paracardiac emphysema parallel to the left heart border.

Fig. 4b. Same case as in fig. 4a. Lipiodol in the descending bronchi, to show that they are not concerned in the shadow complex of paracardiac emphysema.

Physiological Considerations: Pulmonary emphysema is a very common condition; it occurs in the majority, perhaps in all adults coming to autopsy. In its earlier stages it is confined to the anterior margins of the upper lobes, the left lung being affected earlier and more extensively than the right. Elsewhere (1) we discussed in detail the preference of emphysema for the paracardiac lung regions. The contractions of the heart exert a ventilatory action on the lung: during systole the neighboring lung lobules expand; the succeeding diastolic dilation of the heart collapses these lobules. This respiratory activity of the heart is increased in cardiac hypertrophy, particularly in cases

Fig. 1

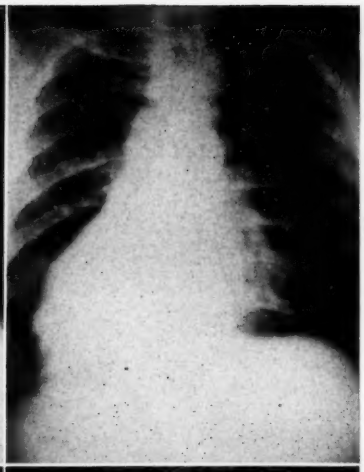

Fig. 2

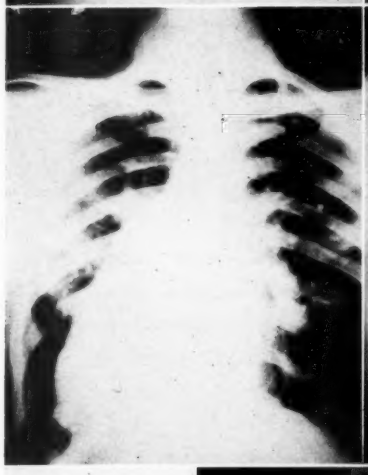

Fig. 3

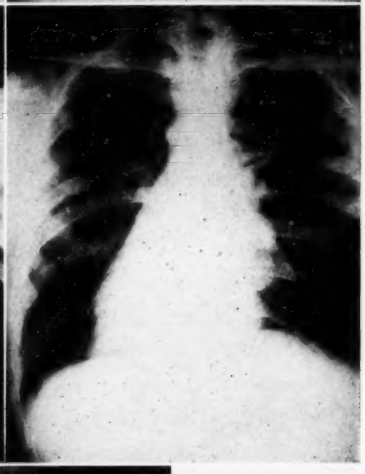

Fig. 4a

Fig. 4b

PLATE 1

of aortic and mitral valve insufficiency, also in the cases of tachycardia and functional hyperactivity of the heart. In these conditions the paracardiac lung regions may be actuated by the heart contractions quite as much or more than by the respiratory muscles. The left upper lobe comes to be the most exercised lung region, and is for this reason the commonest site of emphysema.

The paracardiac emphysema usually produces no symptoms and no marked X-ray changes. Only when unduly developed, generally in association with hypertrophy of the left heart, are the lung changes extensive enough to produce the shadow complex described above.

SUMMARY

In the base of the left lung, parallel to the heart border, there is often observed a sickle-shaped area of increased transparency with a well defined outer border. After several postmortem observations and a study of the cardiorespiratory dynamics, this shadow complex is identified as an expression of emphysema involving the lobules bordering the heart.

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THE RELATION OF INTRAPLEURAL PRESSURES TO THE FORMATION OF EFFUSIONS IN ARTIFICIAL PNEUMOTHORAX[1]

LUCIUS N. TODD[2]

The impression that positive intrapleural pressures are conducive to the formation of effusions in artificial pneumothorax is rather widespread among tuberculosis specialists. It is voiced in the literature and can be heard in almost any discussion of the subject.

In an admittedly incomplete review of the literature, we encountered this impression frequently, but were unable to find much in the way of statistical data to substantiate it. Fishberg (1) feels that effusions are less likely to occur in complete than in partial collapse. He also is of the opinion that the longer pneumothorax lasts, the more certain effusion is to appear.

In contradistinction to this is the statement of Bunta (2) that the largest percentage of effusions appear in association with the largest pneumothorax cavities; 43 per cent of the patients with X-ray evidence of fluid in his series also showing complete or almost complete collapse. In another study he (3) presents some interesting figures, comparing the degree of collapse with the percentage of effusions, and finds that 6 per cent of patients with 5 to 25 per cent collapse had fluid and pressures ranging from minus 10 to plus 6. In patients with 80 to 100 per cent collapse, 59 per cent had fluid and pressures ranged from plus 3 to plus 9. These figures indicated to Bunta that fluid varies directly with pressure. In his series of 860 cases receiving artificial pneumothorax, only 183, or 21.3 per cent, ever showed any evidence of fluid. This is attributed in part at least to negative intrapleural pressures.

Van Horne (4) found fluid more frequently in positive-pressure cases. This he thinks is due, not so much to the pressures, as to the fact that there is a larger pleural space. He strongly favors positive pressures, however, when necessary to obtain satisfactory collapse.

[1] Read before the Southern Tuberculosis Conference and Sanatorium Association, Hot Springs, Arkansas, October 1–3, 1936.

[2] Waverley Hills Sanatorium, Waverley Hills, Kentucky.

Graham, Singer and Ballon (5) state that the reason they have encountered so few effusions is because they always employ small refills and remain on the negative side of intrapleural pressure.

Riviere (6) urges the lowest pressure sufficient to maintain satisfactory collapse, but does not hesitate to employ positive pressures when indicated. He states also that it has been demonstrated that high positive pressures as a rule fall rapidly during the first few hours after a filling.

In an effort to throw some light on this controversial subject we have made a careful study of the records of 215 patients receiving artificial pneumothorax at the Waverley Hills Sanatorium. The majority of these patients have been discharged, and they return to our Outpatient Department for treatment. This group was selected for study because of the length of time they have been receiving treatment, some of them as long as ten years. In addition to these patients, we checked the records of cases still in the Sanatorium, and included all those having fluid and all those having positive pressures, whether they had fluid or not. No case was considered that had been receiving treatments less than six months. Our patients are routinely X-rayed every four to six months while in the Sanatorium and every six months in the Outpatient Department. In addition, they are fluoroscoped at each refill. In our study we not only checked the pneumothorax record with the X-ray; but, to obtain all possible information, we quizzed each patient as to whether or not they had any knowledge as to the presence of fluid at any time. It is surprising to find how closely patients follow their own progress, and we were able to check the record in some questionable instances very satisfactorily with their aid.

In any discussion of intrapleural pressures, it is well to remember that many factors enter into the determination of what is really the true pressure in any given case. Patients with a flexible mediastinum or with hernia will not register pressures under all conditions that will be comparable to those having a fixed mediastinum or paralyzed diaphragm. Posture also has a marked influence on intrapleural pressure, as can be easily demonstrated by introducing a needle into the pleural space and connecting the manometer. Have the patient roll over from one side to the other. A marked elevation will be noted when lying on the pneumothorax side. All of us who are accustomed to administer refills with the manometer open have had the experience of having the patient

cough unexpectedly and force the water out of the tube, showing a high, even if temporary, pressure. It is easy to visualize what happens in

TABLE 1

		per cent		
Total number of patients	215		100	
Number of women	134		62	
Number of men	81		38	
Number of patients without fluid	86		40	
Number of patients with fluid	129		60	
	Without fluid		With fluid	
		per cent		*per cent*
Patients with negative pressure	27	31	64	50
Patients with zero pressure	3	4	10	8
Patients with positive pressure	56	65	55	42

TABLE 2

INTRAPLEURAL PRESSURES	WOMEN									MEN									
	Under 25 years				Over 25 years					Under 25 years				Over 25 years					
	M.A.		F.A.		M.A.		F.A.		Total	M.A.		F.A.		M.A.		F.A.		Total	Grand total
	Right	Left	Right	Left	Right	Left	Right	Left		Right	Left	Right	Left	Right	Left	Right	Left		
Without fluid																			
																			per cent
Negative	6	2	3	2	1	0	1	1	16	2	2	0	0	1	2	3	1	11	27	31
Zero	0	0	0	0	1	1	0	1	3	0	0	0	0	0	0	0	0	0	3	4
Low plus	0	1	1	0	2	2	1	0	7	0	0	0	1	0	1	2	1	5	12	14
Moderate plus	3	2	1	4	1	4	1	5	21	0	0	0	4	2	0	1	2	9	30	35
High plus	1	2	1	1	1	1	2	1	10	0	0	2	1	0	0	0	1	4	14	16
With fluid																			
Negative	6	7	6	6	4	4	5	4	42	2	3	1	1	3	1	4	7	22	64	50
Zero	0	0	1	0	0	1	0	2	4	0	0	0	1	1	0	2	2	6	10	8
Low plus	0	0	0	3	0	3	0	0	6	0	1	2	1	1	2	1	4	12	18	14
Moderate plus	1	1	1	2	0	0	4	6	15	1	0	1	1	2	0	2	0	7	22	17
High plus	2	1	0	2	0	1	2	2	10	0	0	0	3	0	0	2	0	5	15	11
Total	19	16	14	20	10	17	16	22		5	6	6	13	10	6	17	18		215	

Note: Low plus = Under plus two; Moderate plus = Under plus eight; High plus = Over plus eight. Corrected manometric readings.

patients even with negative pressures who do an excessive amount of coughing.

In presenting this study, we wish to make it clear that we do not intend to convey the impression that we have recorded every effusion, however slight, which occurred in these patients. Not an inconsiderable number of cases will show a small collection of fluid in the costophrenic sulcus, which is evanescent and possibly is only observed at a single fluoroscopy. We do feel, however, that we have not overlooked effusions that were enough to alter pressures or remained present for at least a month.

Table 1 epitomizes the results of our investigation. It will be seen that 35 per cent of the patients without fluid had zero or negative mean pressures as compared to 58 per cent of those with fluid, leaving 65 per cent without fluid showing positive pressures as against 42 per cent in the fluid group.

Table 2 gives a detailed analysis of the figures, dividing the patients according to sex, age, stage, side and pressure. The subdivision of the positive-pressure cases was purely arbitrary but gives considerable aid in evaluating the results. Quite a few of the patients in the high-pressure group had pressures too high to be measured by the water manometer. Of this group, 16 per cent without fluid had high positive pressures as against 11 per cent with fluid.

CONCLUSIONS

A study of 215 cases of artificial pneumothorax has been presented and a comparison made between those having effusions and those having none.

We feel that we are justified in concluding that positive intrapleural pressures are not conducive to the formation of effusions, and personally we never hesitate to employ them when indicated.

This study strengthens the impression that we must look elsewhere for the principal causative factors in the production of effusions and we are in agreement with our associates (7) on this point.

It is our intention to present statistical data upon other mechanical factors which might possibly play a part in the formation of effusions in a future study.

We wish to express our appreciation to Miss Rena Washburn, R.N., for invaluable aid in the correlation of the statistical data.

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TRANSTHORACIC TREATMENT OF TUBERCULOUS CAVITIES[1]

A Preliminary Report

M. JACOBS AND H. M. BELOFF

The cavity in tuberculosis of the lungs is a focal point upon whose adequate treatment hinges, to a great extent, the fate of the patient. The existence of excavation is a large factor in the determination of the applicability and type of surgical therapy, and there is no more important gauge of the efficiency of treatment in pulmonary tuberculosis than the progress or regression of cavities. This acknowledged importance of cavities in relation to the pathological course, clinical prognosis, and the success of the collapse therapy in pulmonary tuberculosis, is mentioned because the procedure we are describing has for its purpose the direct treatment of cavities.

The local attack of a tuberculous cavity without recourse to surgical interference is not new. Old tuberculous cavities have been treated by the laryngeal route with metaphen-in-oil (Jacobs (1)) and in the last few years the bronchoscopists have occasionally succeeded in closing cavities by producing a stenosis of the terminal end of the bronchus communicating with a cavity. By their method the tissues around the cavity became atelectatic and ultimately the cavities were closed. However, the procedure we are about to describe differs from the methods mentioned above.

In our method we attempt to attack the cavity directly through the chest wall, injecting colloidal copper morrhuate into it. Ameuille and Durbois (2) of France in 1930, MacDowell (3) (4) of Brazil were the pioneers in attempting transthoracic injections of tuberculous cavities.

The precise mode of action of the copper morrhuate, while not altogether determined, appears to depend in its greatest degree on the stenosis of the bronchus draining the cavity. There is a chemical pneumonitis set up in the pericavernous parenchyma which may play

[1] From the Eagleville Sanatorium, Eagleville, Pennsylvania.

some part in the healing process, as may also the constitutional effect of the copper, a heavy metal, when absorbed into the blood-stream.

INDICATIONS

Transthoracic injection is not the procedure of choice in the eradication of any previously untreated cavity. It is admittedly a method to be used when other treatments have failed.

The cavity must be easily accessible. Most easily reached are those cavities adherent to the chest wall. In the three cases to be reported, the cavities were adherent to the anterior chest wall in the upper lobe in two cases, and to the posterior wall in the lower lobe in the third case. Close examination of chest roentgenograms taken from several angles may be necessary in order to determine whether the anatomy of the cavity is such as to be within reach of a 3-inch needle. Roentgenograms taken with the patient in the anticipated operative posture help localize the site of penetration of the chest wall.

The cases best suitable are solitary large cavities. Where there is multiple cavitation or honeycombing of a lobe with small cavities, the injection of the drug into any one such lesion will not help.

Chronic cavities, surrounded by relatively clear parenchyma, are more ideally suitable for injection than recent cavities, especially where, in the latter case, the adjacent parenchyma is the site of bronchopneumonic tuberculosis. A thin capsule of the cavity is more easily dealt with than a heavy thick one. Where the diagnosis is possible roentgenologically and from the clinical evidence (sputum analysis: presence of elastic fibres, caseous particles, highly positive sputum of considerable volume), a cavity with a fibrous wall would appear a safer type of lesion for injection than one with a necrotic caseous wall.

CONTRAINDICATIONS

As previously stated, the existence of multiple scattered tuberculous cavities contraindicates the injection of a single cavity.

Where there is a heavy infiltrate of pneumonic type about the cavity, so that it will be necessary to traumatize such an area by the needle during the operation, we feel that the dangers are multiplied and the procedure should not be attempted. In needling the cavity, the first trial is not always successful, and successive needle thrusts through an area of pneumonic infiltration presents the danger of carrying the infection into previously uninvolved tissues, and even introducing a notable number of organisms into the blood-stream.

METHOD

Our cases were done with the patient lying horizontally on the fluoroscope table. The roentgenologist fluoroscopes the patient and notes on the skin the position at which the puncture should be made and the direction to be taken by the needle. The skin about the site is prepared with antiseptic solution (iodine and alcohol are used by us), and the area draped so as to give a field as sterile as possible.

The skin is then anaesthetized with 1 per cent novocaine. The operator has been prepared and gowned as for any operation where sterility is essential. A spinal needle is used for the puncture. This is attached to a 10 cc. syringe carrying novocaine, and the needle is pushed through the skin, thoracic wall musculature and pleura, the novocaine being injected as the needle is advanced. When it is judged the needle has traversed the pleura, traction instead of pressure is made on the piston of the syringe, so that, if the needle enters the gas-filled cavity, it will be recognizable by withdrawal of gas into the syringe.

When it appears certain that the needle has entered the cavity, by entrance of gas into the syringe and by a sudden diminution in resistance to further progress of the needle, the syringe is removed, the trocar of the spinal needle replaced, the operative area covered by a sterile towel, and the patient again fluoroscoped to make sure that the point of the needle has entered the cavity. If this has not occurred, the direction in which the error lies is noted, and the needle withdrawn until the point is within the tissues of the thoracic wall, and the new direction taken. This procedure by trial and error, checked by fluoroscope, is carried out until the needle point unquestionably is lodged within the cavity.

The first dose of colloidal copper morrhuate that we have used is 2 cc., injected through the needle into the cavity. Subsequent injections are from 10 to 20 cc., the increase depending on whether the preceding dose was well tolerated. Injections are made at weekly intervals, and the series of injections we have used total six.

When the drug is introduced, it frequently causes a mild paroxysm of coughing, and small quantities of the drug are then expectorated, causing a characteristic taste in the mouth which our patients have described as similar to that of codliver oil.

Following the injection of the drug, the patient is immediately placed in the head-elevated position on the movable fluoroscope and kept there for ten minutes, then sent back to bed.

REACTIONS

In approximately twenty injections which were made through the thoracic parietes, we have only one notable reaction. One patient developed a temperature that fluctuated between 100° and 102°F., beginning 24 hours after the cavity had been injected, extending over a period of four days, after which the temperature remained normal. During this febrile period the cough and expectoration were increased, but these symptoms subsided coincidently with the fall in temperature. After this period had been passed, the patient was examined fluoroscopically and no alteration in the pathology was noted. Our diagnosis was a nonspecific pneumonitis, perhaps chemical in nature, rapidly transient in its course.

CASE REPORTS

A. D 'A., white, male, 27 years old, admitted June 9, 1935, with cough, expectoration and intermittent haemoptysis of six years duration. Sputum on admission was positive (Gaffky IX); its volume in 24 hours was 130 cc. *X-ray on admission* (figure I): *Right:* The upper lobe is practically completely excavated, as is also the lower lobe. The rest is atelectatic and cirrhotic, and the entire pleura on the right side is very thick. The mediastinal structures and heart are markedly deviated to the right. The cavities are patent, made up of thick, fibrogranular walls, and quite well drained. *Left:* There is a minimal fibroproliferative tuberculous infiltration in the superior retrohilar portion of the upper lobe, with a "spill-over" bronchitis in the left lower lobe behind the heart. There is a minimal nonulcerative tuberculosis of the larynx. The temperature was elevated and of a hectic type, varying from 97.6°F. to 100.2°F. each day, with occasional exacerbations of temperatures of 101° and 102°F.

The patient was placed on strict bed-rest, and collapse therapy considered but ruled out because of the notable dyspnoea on slight exertion. The patient remained practically in this same state of severe toxicity to December, 1935. The sputum during these months was highly positive and the volume in 24 hours varied from 105 cc. to 140 cc.

In December, 1935, the injection of the cavity in the right upper lobe was begun, the patient receiving four injections of colloidal copper morrhuate transthoracically, at weekly intervals, under fluoroscopic control. The first injection was 10 cc., the others 20 cc., a total of four injections being given. The following changes have been noted in the patient since this therapy was administered: (1) The 24-hour volume of sputum is now less than half of that previously expectorated. The cough is proportionally reduced. (2) The temperature is less hectic than previously, rising no higher than 99°F.

at any time, and during many days the temperature is altogether normal. (3) The patient is subjectively better. The sputum remains heavily positive. The roentgen appearance of the chest is not markedly altered except for increased density and cirrhosis in the already heavily fibrotic pericavernous tissues of the right lung (figure II).

Comment

This case was chosen, not because it fulfilled our ideal indications for this form of therapy, but because we desired some easily accessible cavity upon which to standardize our technique. We feel that this patient

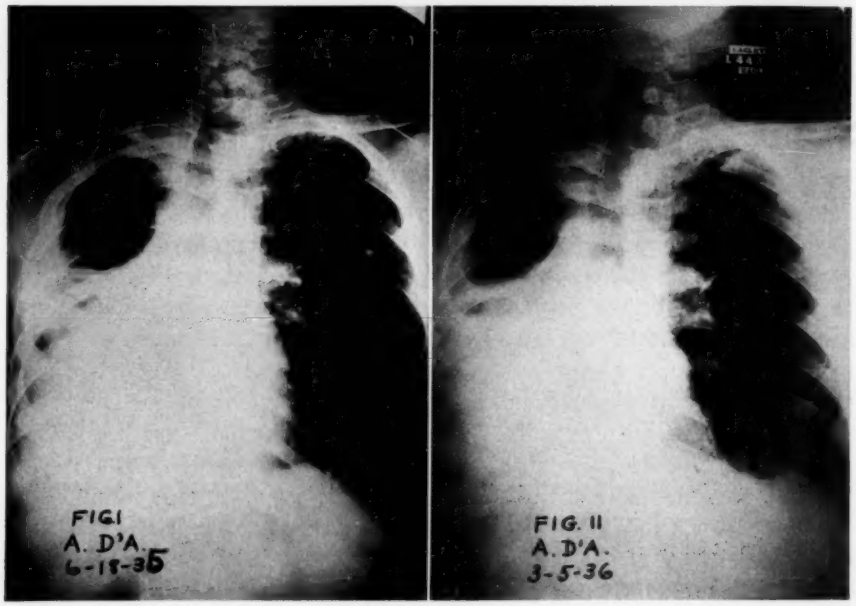

PLATE 1

For description see text.

has been somewhat improved by the injections, but do not think we have altered the ultimate prognosis. This patient is now awaiting thoracoplasty, which will be done after he has passed his extended toxic phase.

C. A., white, female, age 25. Admitted July 9, 1934, with cough and expectoration of several months' duration. Right artificial pneumothorax had been started three weeks before admission. *X-ray on admission: Right:* Pneumothorax present, with complete collapse of upper lobe, and about 30 per cent collapse of middle and lower lobes. However, cavity in the apex of the

lower lobe (3 cm. diameter) is very little compressed. *Left:* Normal. Sputum was positive (Gaffky VII), volume in 24 hours varied from 50 to 100 cc. Weight was 4 pounds below standard. Temperature was slightly elevated each day, to a maximum of 99.6°F.

The artificial pneumothorax was abandoned after 18 insufflations, there being no appreciable effect on the cavity. A right phrenicectomy was performed in November, 1934, and while the diaphragm was elevated and paralyzed as a result, no alteration occurred in the cavity. The sputum remained positive. In June, 1935, the roentgen status was as follows (figure III): *Right:* There is a small cavity 1.5 cm. in diameter at the apex of the upper lobe, and a 7 cm. cavity in the apex of the lower lobe. *Left:* A minimal exudative tuberculous infiltration had developed in the lower lobe, undergoing resolution, fibrosis and also slight focalized excavation. In March, 1935, an attempt was made to stenose the right lower stem bronchus by the introduction through the bronchoscope of 25 per cent acid acriflavine solution. However, in spite of these surgical procedures, the sputum remained heavily positive, and the 24-hour volume was from 50 to 60 cc. The temperature still exhibited its moderate instability.

Transthoracic injection of colloidal copper morrhuate was then advised. The first injection was given February 28, 1936, and the patient has been given four injections to date (April 3, 1936). She has had a moderately severe febrile reaction to two of the injections. The following changes have been noted since the use of this form of treatment: (1) The amount of sputum has been greatly reduced, the 24-hour volume now being only 3 to 6 cc. The sputum however is still positive. (2) There has been very definite improvement in the roentgen appearance of the chest. The cavity is not notably reduced in size but the parenchymal processes scattered throughout the right lung have completely disappeared and the wall of the cavity is thinner and more fibrous (figures IV and V).

Comment

We feel that there is real evidence that this patient has been notably improved by the injection of her cavity.

DISCUSSION

This paper is in the nature of a preliminary report, and given not to present a huge series of cases treated in this manner, but to bring the procedure to the attention of phthisiologists, so that it may be used more universally, and its practicability tested. It is easy to find cases of isolated cavities, not responding to less drastic forms of collapse therapy, in which transthoracic injection may be employed. The technique is

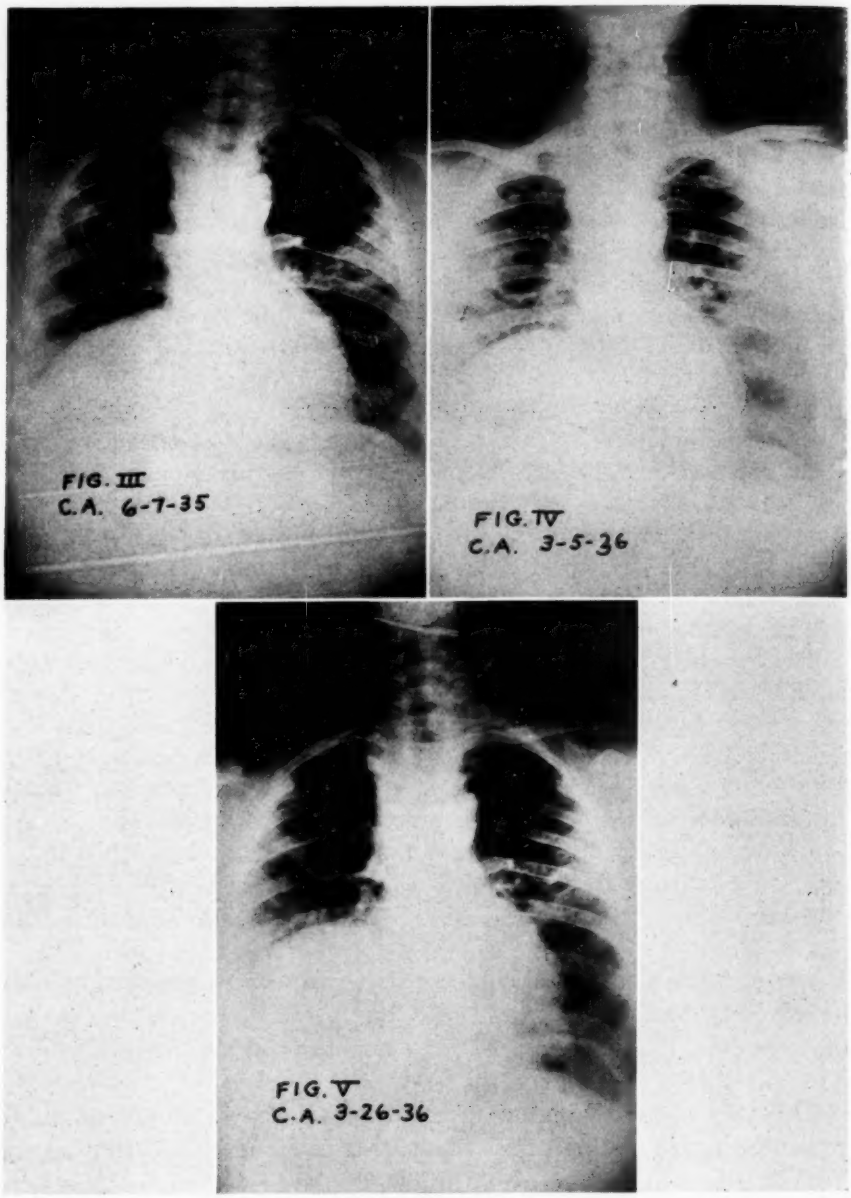

PLATE 2

For description see text.

not difficult, but requires expert fluoroscopic guidance. We do not believe it a dangerous manoeuvre. The prognosis of cavernous tuberculosis is not good, as has been repeatedly demonstrated, and the five year mortality is astoundingly high. Any effort to eliminate the tuberculous cavity therefore has its justification in the mortality statistics for tuberculosis, and we urge that a procedure as simple as we have described, with potentialities for improvement, be more widely employed.

The authors wish to take this opportunity to express their gratitude to Dr. J. Gershon Cohen, roentgenologist to Eagleville Sanatorium, for his excellent and painstaking fluoroscopic work in connection with these cases.

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ACACIA SOLUTION IN THE TREATMENT OF PULMONARY HAEMORRHAGE

OSCAR BERGHAUSEN

Subcutaneous injections of an aqueous solution of gelatin have frequently been used in the past to control recurring haemorrhages. Such injections are painful, frequently lead to abscess formation, and cause albuminuria. Intravenous injections of sterilized gelatin in 25 to 40 cc. amounts of the 10 per cent aqueous solution have also been used, although leading to increased coagulability of the blood. No satisfactory explanation of this action of gelatin has been offered.

In 1915 Hogan (1) reported the successful use of 2.5 per cent gelatin solution in several injury cases and cases of shock following operations. Previously Czerny (2) had concluded that considerable amounts of acacia solution could be injected into normal animals without apparent injury. Bayless (3) introduced the intravenous injection of acacia solution for the treatment of wound shock during the World War and since then the method has been used rather generally. In 1921 Farrar (4) showed that 6 per cent acacia in 20 per cent glucose solution given at a slow rate intravenously is an aid in the maintenance of blood-pressure.

Experimental work by Andersch and Gibson (5) showed that 60 per cent of the acacia was retained by the liver and a smaller proportion by the spleen, kidney and muscles, following repeated injections of gum acacia solution into rabbits. In 1933 Hartman (6) reported favorable effects following twenty-seven intravenous injections of 30 gm. acacia in 500 cc. physiological saline solution, given to six different patients suffering from lipoid nephrosis. However, Andersch and Gibson (7) raised the question whether acacia should be given routinely to patients suffering from lipoid nephrosis and other conditions or whether it was a measure to be used when other methods had failed.

In 1932 the writer was asked to see a patient suffering from advanced pulmonary tuberculosis. She was too ill to have the newer surgical methods employed, and furthermore did not wish them employed. In August, 1933, she suffered from repeated severe pulmonary haemorrhages which ceased following the intravenous injection of 60 gm.

acacia in one liter of physiological saline solution given in two injections. There was no recurrence until June, 1936, when the patient failed rapidly after a severe haemorrhage.

Case 1

Miss A. S., aged 37, single, had haemoptysis in March, 1928, and at intervals thereafter. An X-ray examination in August, 1932, showed involvement at both apices and small cavities, especially marked in the upper left lobe with extensive infiltration of the left lower lobe. In August, 1932, dry pleurisy developed over the right base. On August 29, 1933, she had severe haemoptysis, repeated attacks, at times bringing up a cupful of blood. The usual remedies, including morphine sulphate given hypodermically and fibrogen internally, did not prevent a recurrence of severe haemorrhage. On August 30, 1933, 500 cc. of acacia solution was given intravenously with no general reaction. There was a recurrence of the haemoptysis on the second day, when a second injection of 500 cc. was given. With the exception of slightly blood-tinged sputum a few days later, there was no recurrence of the haemorrhage until her final illness in 1936. Ten days after the injection a maculopapular eruption appeared over the chest and abdomen. The eruption was scattered and accompanied by itching; lasted a week when desquamation occurred, leaving a reddish mark which faded gradually; apparently an allergic skin reaction following the injection of acacia.

Encouraged by this first result the writer did not hesitate to advise similar treatment in a second patient who had repeated pulmonary haemorrhages which could not be controlled by rest and the use of morphine given hypodermically and fibrogen internally. Apparently the patient had numerous haemorrhages before a physician was consulted. He was fond of working in his garden and frequently resorted to heavy lifting; the first haemorrhage followed such strenuous exertion. Although he had no elevation in temperature and the sputum examination for tubercle bacilli was negative, the diagnosis of pulmonary tuberculosis seemed justified after ruling out other possible causes of haemorrhage. The haemorrhages ceased two days after a single injection of the acacia solution.

Case 2

A man aged 63 had been expectorating blood several weeks before Dr. H. H. Schulze was called on June 19, 1936. As much as a cupful of blood at a time was expectorated. It followed the lifting of a heavy barrel. Although there was no elevation in temperature the physician suspected the presence of pul-

monary tuberculosis and had an X-ray examination made by Dr. Chas. Goosmann who reported infiltration of the right middle lobe with increased bronchial tree markings extending upward to the right apex. There was no evidence of cavity formation; the aortic shadow was broader than usual. He suspected the presence of tuberculous infection but stated that an infarct might produce this same wedge-shaped shadow. With the recurrence of a severe haemorrhage on June 29, 30 gm. of acacia in 500 cc. physiological saline solution was given intravenously. This was followed by a chill within 30 minutes and then an increase in temperature to 103 °F. which lasted but a short time. Only two slight haemorrhages occurred, the last one two days after the injection. From then on morphine sulphate, $\frac{1}{4}$ grain, and atropine sulphate, $\frac{1}{150}$ grain, were given subcutaneously once or twice a day; hypodermic injections of obstetrical pituitrin, 8 M each; three injections of $\frac{2}{3}$ grain emetin hydrochloride; calcium gluconate was given internally. On July 7 all medication except the calcium gluconate was discontinued. To date there has been no recurrence of the haemorrhage.

SUMMARY

Two cases of severe recurring pulmonary haemorrhage are reported in which the intravenous injection of 30 gm. of acacia in 500 cc. of physiological saline solution was followed by a cessation of the haemorrhage.

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TUBERCULOUS PERITONITIS [1,2]

LORENZ W. FRANK

Tuberculous peritonitis either as a complication of pulmonary tuberculosis, or as the only clinical manifestation of tuberculosis, is a comparatively rare finding. However, in association with tuberculous enteritis it is relatively common. It has been noted that this condition often occurs when there is tuberculous involvement of other serous surfaces, notably the pleura. At the Colorado General Hospital there have been only three cases proved by autopsy or operation from 1924 to date. The Pathology Department of the University of Colorado has studied the autopsy material of 29 cases at the National Jewish Hospital showing tuberculous enteritis as a complication of pulmonary tuberculosis. Local peritoneal involvement was present in most of these cases. They found tuberculous peritonitis as the only complication in three cases. At this institution we have had four proved cases in which tuberculosis of the peritoneum was the only complication in a period of twenty years. It is more than likely that many cases occur in which the presence of this condition cannot be demonstrated clinically. Many tuberculous patients present symptoms that are suggestive, but since the condition usually runs a mild course and tends to heal, it cannot be proved. The incidence of tuberculous peritonitis seems to be decreasing. Olcott and Paccione (1) studied a series of 109 proved cases of tuberculous peritonitis, 90 of which were diagnosed clinically and 19 of which were found by necropsy. The average age of the seventy women in the entire series was 23.1 and of the thirty-nine men, 30.1 years. Of the clinical cases 73.8 per cent were found in women, while the necropsy incidence was rather higher in men (after allowing for the higher rate of necropsies in the male). It is generally stated that the disease is twice as common in females as in males and that it usually occurs between the ages of 20 and 40.

Whether the process is ever primary or not is problematic; if it occurs

[1] From the Lutheran Sanitarium, Wheat Ridge, Colorado.

[2] Read at a meeting of the Denver Sanatorium Association, Denver, Colorado, May 26, 1936.

with intestinal involvement this might be the case, the infection passing from the intestines. In connection with miliary tuberculosis or other haematogenous spread, it is not uncommon to find tubercles on the peritoneum. The fallopian tubes are more often secondarily involved from the peritoneum than *vice versa*. The appendix, prostate or seminal vesicles may be the starting point or the infection may be spread from a softened peritoneal lymph node.

There are two main types of the disease, the exudative, accompanied by ascites, and the plastic type in which the intestines are matted together, their walls are thickened and the omentum may be rolled into a mass. This forms tumor masses which may be mistaken for other conditions such as tumors. The effusions are rarely large and are often sacculated by the matted abdominal viscera. Such a condition is a combination of the two types of the disease. The ascitic fluid may be haemorrhagic. Enlarged peritoneal lymph nodes (*tabes mesenterica*) are sometimes present and may be a part of the plastic abdominal masses. The peritoneum is usually studded with small gray granulations, which at times seem to penetrate the intestinal wall. They are constantly present on the serous surface of tuberculous ulcers of the intestines. Both visceral and parietal peritoneum may be greatly thickened.

Symptomatology: There is a great diversity of symptoms. The disease may be latent and discovered accidentally during operations. There may be low-grade fever or long periods of subnormal temperature. Otherwise, the patient may be asymptomatic, robust and well nourished. Indefinite gastrointestinal symptoms may be present, such as slight nausea, constipation or even obstruction, requiring operation. At other times, the disease begins suddenly with a chill followed by high fever and leucocytosis. The fever may reach 103° or 104°F. This is accompanied by abdominal pain which at times is so severe as to simulate acute appendicitis, cholecystitis, obstruction or strangulated hernia. The cases with slow onset may be mistaken for typhoid fever. Acute exacerbations may occur at long intervals, the whole process lasting months or years, ending in complete recovery or developing the more advanced lesions, such as tumors, due to thickened intestinal coils or rolls of omentum. Recurring ascites is also common. The larger plastic accumulations may caseate and ulcerate, a seropurulent or purulent exudate follows; this may be sacculated and secondarily infected. Alarming symptoms of toxicity result from such a state of affairs. This disease may at times occur in association with cirrhosis of the liver, ovarian

tumors, trauma or in hernial sacs; when this occurs the picture is still more complex.

Differential diagnosis is difficult. Local signs are deceptive. It is easy to confuse this condition with ovarian cysts or with malignant masses and ascites resulting from a papillary ovary or an adenocarcinoma of the ovary. These conditions are usually not accompanied by fever. Differentiation from cirrhosis of the liver, Banti's disease or chronic nontuberculous peritonitis must also be considered. Here the intracutaneous tuberculin test and guinea-pig inoculation, as well as a history of old tuberculous lesions, are helpful. If there is an associated salpingitis or if there is tuberculous involvement of the lungs, pleura, pericardium, epididymis or seminal vesicles in a patient who has irregular periods of fever and indefinite gastrointestinal symptoms, tuberculous peritonitis should be suspected.

X-ray: There are no distinctive roentgen signs in this condition. However, a flat film of the abdomen without contrast media may reveal dilated coils of intestines which may point the way to the recognition of lesions which are producing partial or complete obstruction. The barium meal or enema may show filling defects or abnormalities of motility. These indirect signs may be helpful in arriving at a diagnosis.

Prognosis: According to Bernhard (2) the mortality in all cases of tuberculous peritonitis, irrespective of their type, was 5 per cent. Mayer (3) says that the serous exudative type generally responds to light irradiation, both in children and in adults. The dry proliferative form, usually adhesive, is more refractory. When there have been ulcerations and large caseous lymph nodes, as commonly seen in children, the results are most unsatisfactory. When the disease is of long standing, healing is more difficult than when irradiation is begun a short time after onset.

Treatment: It is difficult to evaluate the results of any form of special treatment in a disease which often runs a mild course and probably heals many times spontaneously. Many cases seem to recover with rest and general measures alone. Heliotherapy seems to be the most widely accepted form of special treatment, and certainly has a marked effect in the relief of pain and other abdominal symptoms. However, not all cases bear this form of treatment well; their complaints are at times aggravated, especially if it is applied while the fever is high or while there are other signs of toxicity. Brody (4) has concluded that daily exposure to sunlight for a period of from 3 to 6 hours, as has been

prescribed heretofore, is excessive. This agrees with our experience and we have reduced the time of exposure considerably.

Roentgen therapy is useful in some cases. If a focus of infection such as an appendix or fallopian tube can be demonstrated, its surgical removal may lead to a cure. Surgery must also be resorted to in cases of intestinal obstruction.

Merely opening the abdomen has often resulted in a clinical cure, particularly in cases associated with ascites. This can also be said of pneumoperitoneum.

COMMENT

From a diagnostic point of view it should be emphasized that tuberculous peritonitis is a condition which is difficult to diagnose clinically. As a pure complication of pulmonary tuberculosis it is not often recognized clinically, at least not until it is advanced. This is due to its protean clinical course and symptomatology. The frequency with which it is found in association with tuberculous enteritis demonstrates that it is much more common than it is ordinarily thought to be.

Unexplained abdominal symptoms occurring in cases of pulmonary tuberculosis undoubtedly are often due to this condition. Spontaneous healing probably occurs often. Since progression of pulmonary lesions may occur while the peritoneal condition improves, and *vice versa*, frequent and complete examinations are necessary in order to remain fully informed about the course of the disease.

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MANIFESTATIONS OF UNDULANT FEVER IN THE RESPIRATORY TRACT

OREN A. BEATTY[1]

The increase in number of cattle and hogs, together with long distance transporation, has increased their morbidity rate of Bang's disease. Bang's disease has become such a problem that the United States Department of Agriculture has begun a nation-wide project of Bang's disease testing and eliminating reactors in cattle. The number of reactors in the United States during 1935 was 13 per cent of 3,300,000 cattle. The number of reactors to Bang's disease exceeded the number of tuberculin reactors, although more than 25,000,000 tuberculin tests were applied. This suggests a tremendous probable source of infection in those that have not been tested. When this is generally realized *Brucella* infection in man will be given more consideration. Undulant fever in man was once considered a rare condition but has become more prevalent in the past decade and at the present time is a major public-health problem.

Very little has been written in this country in regard to symptoms of this disease referable to the respiratory tract, expect in a general way. Bogart recently called attention to the sparsity of reports of pulmonary manifestations and reported four cases of undulant fever in which pulmonary symptoms occurred with demonstrable roentgenological changes. This is a study of forty-seven cases of undulant fever with particular reference to respiratory symptoms and an X-ray study of twelve cases.

SYMPTOMATOLOGY

In general, two forms of undulant fever may be recognized, the acute and the chronic. The literature gives other finer distinctions but most cases are readily grouped into acute or chronic. In the acute cases the onset may be gradual with malaise, general aches and pains, backache, and aching in the back of the neck, and chilliness at times. These symptoms may progress into acute conditions; or the onset may be with

[1] Chest Clinic, T. J. Sampson Community Hospital, Glasgow, Kentucky.

severe chills and fever of 103° to 104°F. and complaints of general aches and pains; particularly backache and aches in the back of the neck. Many patients complain of aching in all parts of the body, even in skin, teeth and scalp; and many complain that the skin of the neck is so sore that merely touching it is very painful. Marked loss of weight and severe night-sweats characterize the acute stage. The acute stage may last from two weeks to two months with exacerbations and remissions of pains and fever, but I have not observed that the exacerbations and remissions occur at any particular time of the day. In many patients who are not aware of fever the temperature ranges from 103° to 104°F.

The chronic stage may follow the acute and may last for several years. It may be characterized by backache, aches in the back of the neck, choking or smothering sensations at times, palpitation at rest or on exertion, fatigue on exertion, extreme nervousness, pains in shoulders, along rib-borders, or in the region of the ovaries, and inability to do a day's work. These symptoms also occur in periods of exacerbation and remission and may or may not be accompanied by fever. In some cases of proved chronic undulant fever there has been no acute stage according to the patient's history. The above symptoms of the chronic stage are observed in the majority of cases, but there are innumerable other symptoms observed in individual cases. It is in the chronic stage that so many present themselves for chest examinations. These cases are characterized by burning sensations and pains in the chest, cough without expectoration or with mucoid or mucopurulent expectoration, occasional haemoptysis, fatigue on exertion, inability to perform a day's work, hoarseness, afternoon fever and night-sweats; they are convinced that they have pulmonary tuberculosis or some other pulmonary disease. Undulant fever manifests itself practically throughout the respiratory tract, particularly in the bronchi and the larynx.

Of forty-seven cases diagnosed as undulant fever, thirty-two were studied sufficiently to tabulate their symptoms. Of these, thirty-one had symptoms referable to the respiratory tract: eighteen had cough, sixteen expectoration, five haemoptysis, twenty-six pains in the chest, twelve burning sensations in the chest, twenty-three choking or smothering sensations, fifteen weakness of voice, fourteen hoarseness, five nasal discharge, eight postpharyngeal discharge and seven sneezing. The symptoms referable to the upper respiratory tract were overlooked in the early cases.

DIAGNOSIS

A diagnosis is first suggested by the clinical symptoms and particularly by the absence of physical signs of any other disease. It is important to take a careful history in order to bring out all the symptoms, since the symptomatic manifestations of undulant fever are rather characteristic. There are many diseases with which undulant fever may be confused, particularly tuberculosis, influenza, typhoid fever and malaria. The respiratory symptoms of undulant fever, with afternoon fever occurring in the asthenic type of patient, are easily mistaken for tuberculosis, particularly in the absence of an X-ray plate of the chest and sometimes even in the presence of such an X-ray plate. Frequent attacks of fever simulating influenza in the otherwise healthy individual are often diagnosed as influenza. When attacks of undulant fever occur in the warmer months, and particularly in the presence of outbreaks of typhoid fever, it is often diagnosed as typhoid in spite of negative cultures and Widals. It is not infrequent that patients state they have not been well since having had typhoid fever several years ago. These patients should be examined for undulant fever and, if undulant fever is found, it is reasonable to suppose that the original disease was undulant fever. The acute stage of undulant fever with frequent chills is often called malaria and treated as such. Undulant fever should be in mind in the study of the above four conditions particularly when the diagnosis cannot be confirmed readily by the ordinary laboratory aids.

The agglutination and intracutaneous skin tests are invaluable laboratory aids in making a diagnosis. Ordinarily an agglutination test positive in 1 to 80 dilution or above is considered diagnostic, but so many patients are seen in whom several positive agglutinations below the 1 to 80 dilution are obtained before one in a higher and so-called diagnostic dilution that it seems a positive test in any dilution should receive serious consideration, expecially in the presence of clinical symptoms. Angle states that when the agglutination titre is low or absent the patient may be a victim of this disease. Simpson states that agglutinins are absent in five per cent of the cases. Harris thinks much harm has been done by laboratories stating that only tests in dilutions of 1 to 80 or higher are of significance. He further states that eleven of seventy-five cases he observed were negative on repeated agglutination tests. A positive test in any dilution should call for further diagnostic efforts, and so should a negative test with clinical symptoms. The skin

test may prove to be of more value than the agglutination test, since the agglutinating titre of the blood may change rapidly. The test is made with .05 cc. to .1 cc. of *Brucella* antigen intracutaneously. Pseudoreactions are at their height at twenty-four hours and begin to subside before forty-eight hours. A positive reaction is at its height by the fourth day and should gradually subside and persist in the form of a reddish-brown discoloration for four weeks or longer. In many positive cases of undulant fever in which skin tests are done, an immediate local reaction is obtained which may be a specific bacterial phenomenon, which may have diagnostic significance. Recovery of the organism from the blood-stream is diagnostic, but the procedure is rather difficult to carry out in the ordinary laboratory.

PHYSICAL FINDINGS REFERABLE TO THE RESPIRATORY TRACT

The nasal mucosa has not been examined routinely. The pharynx, in occasional cases, shows moderate or mild injection. The larynx, in many cases, shows injection of the epiglottis, arytenoids, and ventricular folds. This injection may vary from a mild condition to that of diffuse redness with a granular appearance and slight to moderate swelling. The vocal cords are not injected. Physical examination of the chest is negative as a rule in the chronic case. One case reported here had impaired percussion note with deep-seated moderately coarse râles after cough. Bronchiectasis was suspected but not proved. Another case had a few deep-seated fine moist inspiratory râles from the third to the sixth vertebral spine on the left. In acute cases, simulating pneumonia, a small patch of dulness with bronchial breathing and sparse moist inspiratory râles may be found. Also a friction rub may be heard occasionally, especially in the pneumonic cases and those that have pleuritic pains. One case had a pleural effusion.

ROENTGENOLOGICAL FINDINGS REFERABLE TO THE RESPIRATORY TRACT

In a study of the X-ray appearance of the chest of the undulant fever patient we see variations in the amount and distribution of changes from the normal. The most constant change noticed is hilar infiltration with a generalized peribronchial infiltration as shown in figures 1 and 2. In some cases the hilar infiltration may predominate over generalized peribronchial infiltration; and in some the generalized peribronchial infiltration may be greater in one lung than the other or greater in one base than in the other. The next most frequent change noted is pleural.

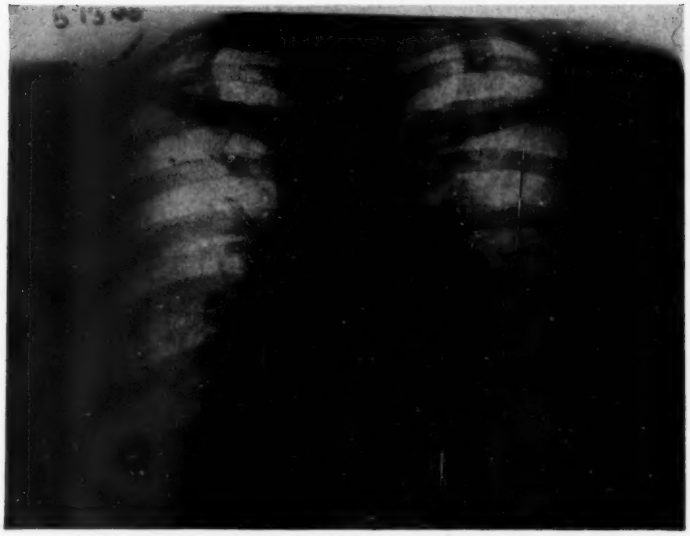

FIG. 1. Generalized peribronchial infiltration throughout both lung fields with moderate hilar infiltration on both sides.

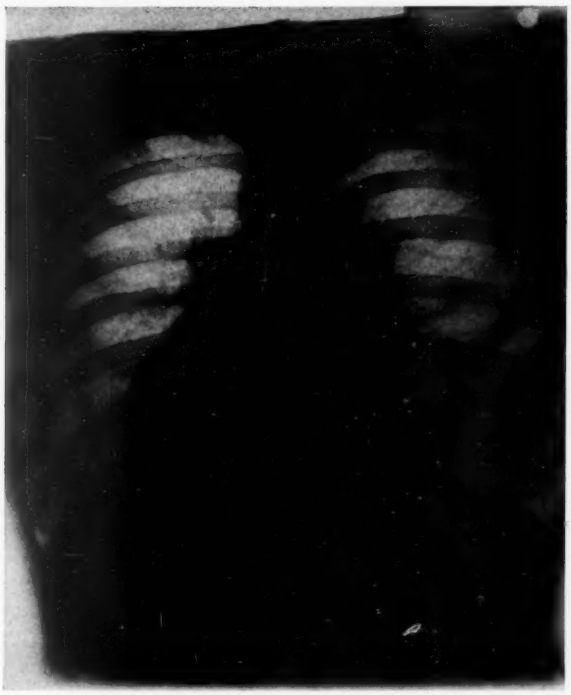

FIG. 2. Generalized peribronchial infiltration throughout both lungs with moderate hilar infiltration on right.

One case of pleural effusion and one case of diaphragmatic pleurisy with adhesions were seen. No X-ray was obtained of the patient with pneumonia during the pneumonic stage.

DISCUSSION

Due to circumstances only twelve, of forty-seven cases, have had X-ray examinations of the chest. One patient is included who could not be definitely diagnosed as undulant fever. Several other patients presented as severe chest symptoms as those who were X-rayed. It is believed that they too may have presented pictures similar to the above. Of these forty-seven cases, thirteen had been previously diagnosed or strongly suspected as having pulmonary tuberculosis. In the majority of cases that present themselves to chest clinics for examination no tuberculosis is found. In nontuberculous chronic chest conditions undulant fever should receive serious consideration in the differential diagnosis. All twelve patients whose chests were X-rayed showed more or less marked enlargement of the hilar shadows and some scattered peribronchial infiltration, usually bilateral and frequently more pronounced in the basal portion.

A history of haemoptysis is not infrequently encountered in these cases of undulant fever. The author did not witness the haemoptysis in any case, but was able to get a definite history of haemoptysis in each case reported. In one case the material expectorated the day following haemoptysis was viewed and this was mixed throughout with old and fresh blood. Haemoptysis occurs frequently enough in the history of these cases to warrant the belief that it may occur in the cases with pulmonary X-ray changes.

Another symptom frequently encountered in the history is hoarseness and weakness or loss of voice. This may be easily explained from examination of the larynx which shows in the majority of the cases examined a definite laryngitis. Sneezing, postpharyngeal discharge and nasal discharge or rhinorrhoea occurred in many of the later cases. These symptoms were overlooked in the first cases encountered, until one long-standing case of rhinorrhoea, which had not yielded to treatment, cleared up when the patient's undulant fever was treated with undulant fever vaccine. This directed attention to the nasal symptoms found in undulant fever.

Another respiratory symptom observed in many cases is a smothering or choking sensation. If this condition is severe many patients

think they are going to die, and afterwards say they could not live through another attack. The severity of the attack impresses witnesses and onlookers. To the witnessing physician there is not the respiratory difficulty that is observed in a severe attack of asthma or severe cardiac condition. The concurrent cyanosis is not typical and it is a rather murky or dirty cyanosis. Palpitation is complained of and tachycardia is present during the attack. The attack may last from thirty minutes to two hours or longer and may simulate effort syndrome but it is probably more severe in many cases.

CONCLUSIONS

1. Undulant fever is a major public-health problem.
2. It manifests itself frequently by respiratory symptoms and signs.
3. Demonstrable X-ray changes are noted frequently, consisting of peribronchial infiltration, thickened pleura, pleural adhesions and pleural effusions. Pneumonias occur but are not demonstrated here roentgenologically.
4. Chronic nontuberculous pulmonary conditions should include undulant fever in the differential diagnosis.
5. Undulant fever should receive consideration as the aetiological agent of such conditions as rhinorrhoea, "common colds," influenza, sinusitis, pharyngitis, laryngitis, bronchitis and pneumonia when the aetiology is not definitely known. Haemoptysis may also be included.

Appreciation is expressed to Dr. O. O. Miller, Louisville, Kentucky, for the use of one X-ray picture, and to Miss Mary Foulk, clinical nurse, and Miss Katherine Morrow, technician, for their help in the study of these cases.

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EDITORIAL

The Value of Tomography in the Diagnosis of Pulmonary Lesions

Dr. J. B. McDougall's and Dr. J. H. Crawford's article on "Tomography" (1) with special reference to its value in the diagnosis of pulmonary lesions is most instructive and suggestive. I know of no clearer statement of what Tomography is, and what may be expected of it when studying pulmonary lesions.

Before expressing any opinion I wish to state that it has not been my good fortune to have used the tomograph personally. After working with any instrument one's opinion may change or crystallize.

To those who have had to depend upon single films this will be a great advance. For those who have had the advantage of stereoscopic films it will not be necessary so often.

The bronchial, the pulmonary and the venous systems are beautifully described, but if one wishes to study the normal anatomy of a healthy chest, tomography, in my opinion, cannot compare with good stereoscopic films. This is also true of pulmonary exudates, which must be diagnosed and accurately localized. Such lesions are common in the upper third of the lower lobes, and the trunks to these important areas have not been described in this article. I doubt that they could be shown by tomography.

For many years it has been my privilege to study pulmonary anatomy and pathology by means of stereoscopic films. I have had hundreds of cases come to autopsy. It is daily practice to describe the trachea, the right and left bronchus, the eparterial and the hyparterial bronchus, the pulmonary arteries and to note their dislocation and some of their pathology. With this anatomy as a basis the pulmonary lesions are quite accurately described and localized with regard to the part of the lobe involved. This is accomplished in the vast majority of cases studied. I cannot conceive that this could be done as accurately by tomography as by stereoscopic films.

When dealing with very dense lesions or tissues of homogeneous density stereoscopic films are valueless and it is my hope that tomography will be able to solve the difficulties encountered in such cases. This

is illustrated by case 6, figure 12 (1). When positive sputum persists after thoracoplasty, it is often impossible to localize by stereoscopic films cavities concealed in the dense mass of tissue. The authors have demonstrated that tomography is most helpful in such a case.

We are all indebted to Doctors McDougall and Crawford for this clear presentation of a new instrument and its usefulness.

K. D.

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THE ALLERGIC STATE AND ITS RELATION TO HYPERSENSITIVENESS AND RESISTANCE[1,2]

J. BRONFENBRENNER

Normally the tissues of higher animals are protected against an intimate contact with complex organic substances of the environment by the relatively impermeable barriers of the skin and mucous membranes covering the outer surfaces and body cavities.

Thus, in order to be assimilated, the organic materials must be taken in as food and rendered more diffusible by the process of digestion before they can enter the lymphatics or the blood-stream. In this form, as products of digestion, they possess little or no immunogenic activity.

However, any wilful or accidental break in the efficiency of natural barriers, due to physical, chemical or mechanical trauma or to biological changes which tend to increase permeability of the skin or mucosa, may permit the passage of unchanged complex organic substances into the circulation.

Such an exposure of unprotected tissues to complex foreign substances radically changes their natural responses.

This alteration is specific and entails, in the final analysis, an acquisition of alertness in the reactivity of the tissues as expressed in their increased capacity to immobilize, neutralize and eventually to eliminate the particular foreign matter when it is reintroduced into such an altered organism. Pirquet named this altered reactivity "allergy."

In its original meaning the term "allergy" was intended to denote the fundamental specific alteration in the reactivity of the animal engendered by the parenteral exposure to an antigen, irrespective of the character of the outward expression of this altered reactivity. More specifically Pirquet proposed the term "allergy" to cover the whole range of specifically-altered reactions, whether they took the form of exaggerated reactivity (hypersensitiveness, anaphylaxis) or of apparently diminished reactivity (tolerance or immunity) (1).

[1] From the Department of Bacteriology and Immunology, Washington University School of Medicine, St. Louis, Missouri.

[2] Presented at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

The specificity of this process is mediated by antibodies, which thus may serve as indices of past immunogenic experiences, and if they are produced in sufficient amount to appear free in the circulation, they may be used for a passive transfer of this specific altered (allergic) reactivity to normal tissues.

Because the early investigators were impressed by the fact that as a part of the allergic syndrome accompanied by the production of specific antibodies, the organism acquired the capacity of ridding itself of foreign material which frequently was injurious to the host, this process has been viewed as a protective mechanism and referred to as "immunity," and antibodies as protective.

As a matter of fact, however, this teleological concept of the reaction on the part of an allergic (modified by the previous exposure) animal organism to the parenteral introduction of foreign specific antigen does not adequately fit all the phenomena observed. For while it is generally true that repeated parenteral exposure to toxins or to pathogenic bacteria may eventually render the organism relatively resistant (immune) to these substances, experience has shown that under certain conditions the repeated entry of totally innocuous antigens into a previously exposed organism may produce severe symptoms or even death.

To explain this paradox, some investigators have suggested the possibility of the existence of two sorts of antibodies—one conferring the heightened resistance, the other the heightened susceptibility—but, in view of the lack of evidence to support it, this hypothesis has been given up. At the present time the bulk of evidence indicates that the same antibodies are responsible both for the phenomena of specific hypersensitiveness and of specific resistance. However, there is still no agreement as to the nature of the mechanism determining which of these apparently widely different responses is to take place in a given instance. The more widely prevailing view is that "the difference between the anaphylactic and immune state is quantitative rather than qualitative, depending on distribution of antibody." According to this concept "the anaphylactic state is associated with the presence of fixed antibody and the absence of circulating antibody," and "the immune state is associated with the presence of circulating antibody in a concentration sufficient to protect the fixed antibody that is also present" (2). That is to say, the presence of an excess of circulating antibody confers upon the sensitized animal resistance (immunity), because the antigen by combining with circulating antibody is prevented from reaching the sensitized tissues.

Inversely, if antibody content of the circulating blood of the animal is low, the animal is hypersensitive because the reëntering antigen is not prevented from reaching sensitized tissue and causing the anaphylactic syndrome.

Although, as stated above, this is the prevailing view, much of the available evidence contradicts it most decisively.

The original evidence on which the development of this concept rests was supplied by Weil (3), who observed that sensitized guinea pigs could be protected against shock by a preliminary injection of an excess of antibody-containing horse serum. That the inference drawn by him and accepted as the basis for the hypothesis explaining the paradox was inaccurate follows from a variety of considerations.

In the first place, in postulating that circulating antibody arrests the antigen and prevents it from reaching the sensitized cells, it is necessary to assume also that circulating antibody by some special mechanism is capable of combining with antigen more rapidly, or more effectively, than does the antibody at the cell surfaces; while exactly the opposite assumption is needed to explain the effectiveness of desensitization.

It is clear that if desensitization is due to the fact that antigen reaches the cells and exhausts antibodies at their surfaces (thus rendering them incapable of subsequent uptake of antigen), it is necessary to assume that cells promptly take up the small amount of antigen injected for the purpose of desensitization in spite of the existence of sufficient antibody in the circulation of desensitized animals to accomplish passive transfer of hypersensitiveness to normal animals.

That refractoriness to anaphylaxis following desensitization is not due to the saturation of antibodies at the cell surfaces is indicated also by the fact that animals sensitized to two or more antigens and desensitized with one of them become more resistant to other antigens also. It is evident that lack of response to secondary antigens could not be explained on the basis of exhaustion of the corresponding antibodies either at the cell surfaces or in the circulation.

Moreover, the animals rendered refractory to a given antigen through specific desensitization (which according to the above hypothesis exhausts antibodies at the cell surfaces) will react with acute anaphylactic shock if a relatively large amount of the antigen in question is injected, that is, the refractoriness is only relative and evidently is not due to the saturation of antibody and the lack of capacity of "desensitized" tissues to combine with antigen.

Furthermore, it is well known that refractoriness to anaphylaxis can be induced by a variety of nonspecific procedures and among others by the parenteral introduction of small amounts of many unrelated organic and inorganic substances, some of which in larger doses may by themselves cause symptoms closely resembling anaphylaxis (anaphylactoid). In fact, as has been shown in our laboratory by Morris (4), intravenous injection of normal horse serum is capable of inducing in guinea pigs a certain degree of refractoriness to anaphylaxis in general. These experiments suggest that it was the injection of horse serum as such and not its antibody content that was responsible for the protection of guinea pigs from anaphylaxis recorded by Weil. The experiments of Morris indicated that if, instead of horse serum, as in experiments of Weil, the homologous (guinea-pig) serum is used as a source of additional antibody it is found that the preliminary introduction of an excess of antibody not only fails to protect the animal against the shock, but on the contrary renders it more susceptible, so that it will now succumb with anaphylactic shock to an introduction of a much smaller amount of specific antigen than was necessary before the introduction of additional antibody (4). That excess of circulating antibody does not protect sensitized animals against shock is also shown by the fact that in a series of animals, as for instance in experiments of Jackson (5), the higher the circulating antibody titre of the animal, the more likely is anaphylactic death to ensue following the introduction of antigen. This author has also been able to confirm repeated earlier findings of free antigen in the blood of sensitized animals surviving the test injection, while, in animals dying of anaphylactic shock, he found free antibody present in the plasma after death. It is clear that in these experiments failure of circulating antibodies to bind the antigen and thus presumably exposing the sensitized tissues to it did not cause the shock, and inversely presence of free antibody did not prevent the shock from occurring.

Even this brief review of evidence clearly indicates that distribution of antibody is not sufficient to explain the paradox. In fact, the basic implication of this hypothesis that the circulating antibody takes no part whatever in the causation of shock has been shown to be false. This notion originated largely as a result of two observations. One is that, when guinea pigs are passively sensitized by introduction of antibody, the state of hypersensitiveness usually can be elicited in them only after an incubation period of 4 to 6 hours. The other is that occasionally, especially in man, a state of hypersensitiveness may be elicited in the absence of circulating antibody as tested by usual procedures.

With respect to the first of these observations, it has been shown long ago by several investigators that although in guinea pigs results were less regular, at least in the case of certain other species of animals the incubation period in passively induced hypersensitiveness is not at all essential. Both rabbits and mice react immediately not only to the introduction of antibody and of antigen in rapid succession and in either order of precedence, but also to the injection of the mixture of both reagents. Although the validity of these observations is not questioned, and although they seem to indicate definitely that "meeting of antigen and antibody in the circulation can cause injury," the occurrence of these reactions is considered by some authorities to be in the nature of exceptions, the mechanism of which remains unknown for the present (6), while other authorities, admitting that "our present knowledge of anaphylaxis in the rabbit suggests that reaction of antigen and antibody in the blood may play a predominant rôle," discount the significance of this evidence, ascribing the results to the peculiarity of the rabbit as an experimental animal (7).

However, since several authors have during the last year again elicited in guinea pigs passive anaphylaxis without incubation period, it is likely that the rôle of circulating antibodies in anaphylaxis may be recognized more generally in the future (8) (9).

As to the earlier finding of tissue sensitivity in man in the absence of demonstrable antibody, it has been found more recently that this discrepancy was due to inadequacy of methods employed for the detection of antibodies. By means of the Prausnitz-Kustner technique, the secondary factors which masked the reaction in older experiments can be eliminated and the presence of antibody may be demonstrated with regularity.

Thus we see, as stated above, that much of the evidence contradicts the prevailing notion that balance of the antibody as between the tissues and the blood determines the outcome of the reaction when antigen is introduced into the previously exposed or passively sensitized animal.

How then can the distinction between the "anaphylactic" and "immune" states be explained? For the last 20 years we have held that there is no such distinction (10). Each "immune" animal, irrespective of the relative concentration or distribution of antibodies, will respond with symptoms of hypersensitiveness if introduction of antigen is carried out under suitable conditions designed to elicit this type of response. No matter how much circulating antibody may be present, and irrespective of whether the animal is immunized actively or passively, an immune

animal capable of withstanding many thousand lethal doses of a suspension of virulent pneumococcus will succumb to an acute anaphylactic shock if a relatively small amount of the corresponding type specific polysaccharide is injected rapidly into his veins.

As a matter of fact, whenever antigen-antibody reactions occur *in vivo* there always occurs a concomitant injury to the tissues of the host. The outward expression of this injury may vary in form and in intensity, depending on the time elapsed since the last exposure and the amount and nature (solubility) of antigen, as well as on the site and the rate of its introduction into the sensitized organism. In final analysis, the availability of antigen for a rapid union with antibody determines the intensity of the injury (11). Thus, while a sensitized guinea pig may be instantly killed by intravenous injection of a lethal dose of egg-white, such an animal may survive, showing only mild symptoms, if the same dose of antigen is given subcutaneously or even if given intravenously, but very slowly, yet it will eliminate the injected egg-white more quickly than would a normal animal.

The intimate mechanism of this dual response is as yet not definitely known, but the evidence indicates that the union between the antibodies and the antigen produces a disturbance in the delicate adjustment of the colloidal conditions existing in the blood, as well as at the surfaces of the tissue cells with resulting intensification of physiological processes leading to an increase in the rate of elimination of foreign matter, and at the same time to a liberation of toxic histamin-like split products which affect the tissues of the host (11). Under certain circumstances this accelerated catabolic activity may be purely harmful, as in the case of experimental anaphylaxis or in acute reactions following administration of therapeutic antiserum to individuals possessing antibodies against the protein of the serum. However, these acute reactions are in reality laboratory artefacts which can take place only through wilful or accidental introduction of antigen in solution (or of its specific hapten) past the normal barriers directly into the blood-stream of the immune animal. While under natural conditions, as in the case of exposure of a previously exposed or vaccinated (immunized = sensitized) animal to reinfection, the entrance of a relatively minute amount of antigen in the form of an invading microbial parasite causes acceleration and intensification of catabolic activity, setting up a local reaction which may be sufficient in extent to arrest the penetration of the antigen beyond the point of entry, while causing only a minor degree of injury to the host tissues and pro-

ducing only mild, indefinite, systemic symptoms seen in abortive infections. The advent of bacteriolysis and of phagocytosis may eventually eliminate the antigen altogether, and we think of the whole process as a purely defensive one, quite disregarding the concomitant injury to the host tissues.[3]

Thus it seems that so far as our present knowledge goes, the phenomena of experimental anaphylaxis, of clinical hypersensitiveness and of specific acquired resistance to infection are all the result of a single underlying mechanism, the character of the total observable reaction being determined by secondary factors.

Although this "unitarian" concept of allergic phenomena is being accepted by a gradually increasing number of immunologists, many investigators still maintain the dualistic view that hypersensitiveness and resistance are independent of each other and that under proper conditions evidence for each may be secured in the absence of the other. Thus, for instance, Calmette (12) stated that by inoculating guinea pigs with *BCG*, he had been able to detect in them the first appearance of hypersensitiveness to tuberculin in from 8 to 10 days, whereas the resistance to infection with virulent organisms was not established in these animals until about a month after the sensitizing *BCG* injection. Thus, he thought that over a period of about 20 days the animals exhibited hypersensitiveness without resistance to infections. The evidence presented in this experiment is not conclusive, however, since the size of the bacterial inoculum used in testing resistance of these animals may have been too large to detect resistance at the moment of the earliest appearance of hypersensitiveness.

Equally inconclusive is the experiment in which Calmette thought he had proved the possibility of producing resistance without the accompanying hypersensitiveness by showing that cattle inoculated with *BCG* remained resistant to infection for several months after the disappearance in them of skin reactivity to tuberculin. It is quite certain that these animals remained anamnestic even though they did not respond to the usual dose of tuberculin, and thus, when virulent bacteria were injected, after a short delay response was elicited localizing the bacteria and protecting the animals against infection. Doubtless a subcutaneous test would have caused a reaction in these animals at any time after the

[3] It is clear that, *mutatis mutandis*, the same reasoning applies to the reactions of sensitized tissues set up by contact with or absorption of unorganized antigens, as in various types of clinical hypersensitiveness.

primary infection, as it does in human beings, if a sufficiently large dose of tuberculin would have been used.

But even if it were possible to show that the local inflammatory reaction may be minimized or suppressed without affecting the degree of specific resistance of the animal, such evidence would not necessarily prove that the two phenomena are independent of each other. For in such instances where the direct (bactericidal) or indirect (opsonizing) effect of antibody upon the antigen constitutes the most essential part of the mechanism by which the progress of infection is arrested, the incidental injury to the host may actually be a fortuitous and even detrimental by-product of the reaction. It is understandable that in such cases the total resistance to infection may not suffer through minimizing the incidental injury to the host tissues. For example, Morris (13) has shown that guinea pigs passively sensitized with anti-Friedlander type "B" serum and desensitized with the specific carbohydrate remain as resistant to infection with Friedlander's bacillus type "B" as undesensitized guinea pigs.

However, in those instances where the resistance to infection depends primarily on the mechanism of localization of antigen by the specific inflammatory reaction set up at the site of its entry, desensitization would be likely to cause definite diminution in resistance to infection. Thus, for instance, in connection with tuberculosis the general opinion seems to be that this allergic tissue reaction as such is the most important single factor of resistance against reinfection. This was particularly clearly shown in the experiments of Willis (14). By means of excision of the site of intracutaneous inoculation, this author prevented the spreading of infection in normal guinea pigs only if the excision was performed not later than 3 hours following injection, whereas in the allergic animals the excision of the inoculated site could be delayed for 7 days without causing the spread of infection to the regional lymph nodes. In addition, there is a great deal of less direct evidence pointing in the same direction. Thus in experimental infection the incubation period required for the establishment of the demonstrable hypersensitiveness to tuberculin is roughly of the same order as that required for the establishment of a relative resistance to reinfection, and the phase of the disease during which hypersensitiveness is demonstrable corresponds, in general, to that during which resistance to reinfection is most evident. So that in animals in which the intense necrotic reaction takes place, reinfection is limited in extent or fails altogether, but where the local reaction is

weak or absent, a progressive abscess results. In the final stages of a progressive infection both the demonstrable hypersensitiveness and the resistance to reinfection disappear at about the same time. Both hypersensitiveness and the resistance require for their existence the continuance of the antigenic stimulus; they both disappear with recovery, and serum of resistant animals fails to transfer either the sensitivity or the resistance to infection, showing that both conditions appear to depend on the coöperation of the host tissues.

This brief review of the subject suggests the conclusion that phenomena of specific heightened resistance and of heightened susceptibility are different manifestations of a single biological process—allergy. The first type of manifestation gives a record of changes as they affect the antigen, the second serves as an index of the changes involving the tissues of the host, both sets of changes occurring in a single event whenever the antigen is reintroduced into the previously exposed (allergic = immune = sensitized) animal.

So long as the intensity of this process is such that the incidental injury to the host remains within the limits compatible with the continuation of physiological processes, the total reaction results in checking the penetration of the antigen and is interpreted as protective. But if secondary factors so modify the course of the reaction that injury to the host becomes incompatible with life, we interpret the process as increased sensitivity.

As a crude analogy one might consider the process of burning of wood in a hearth. So long as the fire is kept within the confines of the fire box and gives us comfortable warmth, we consider the process beneficial quite disregarding the fact that the loss of wood is inseparably associated with it. Occasionally, however, when the fire gets out of control and burns up the entire building, although heat was generated here just as before, we consider the event as destructive.

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RELATION BETWEEN TUBERCULIN ALLERGY AND CLINICAL COURSE[1]

J. M. APPEL, B. H. DOUGLAS, T. R. JOCZ AND H. S. WILLIS

May tuberculin be relied upon as an index of prognosis in tuberculosis? This question has been studied by a number of people, but in general such efforts, although varied, have been disappointing. Several observers have carried out studies that were designed to elicit possible fluctuations in sensitiveness to tuberculin but the results have been far from uniform. And it may be pertinent to question whether such a matter is susceptible of solution in the present state of our knowledge.

That the tuberculin reaction depends upon the allergic state of those tested is agreed to by all. Allergy, for some time thought to be an unchanging concomitant of tuberculous infection, is known to fluctuate in accordance with the age and condition of the infection underlying it. Its degree may be heightened by exacerbation of the disease and (at times) by introduction of tuberculin. It may be lessened in intensity by arrest or healing of the disease, by cachexia, by treatment with tuberculin (which leads to either protein desensitization or fibrous investment and healing of lesions), by intercurrent disease[2] and, theoretically at least, by fluctuations in the patient's reaction to the disease.

Varying results in a study of the fluctuations in tuberculin sensitiveness may depend upon any one of a number of factors, such as: (1) differing bases of interpretation; (2) dosage; (3) technical difficulties, such as depth of injection, volume and age of material injected and the degree of dilution; (4) the possible modification of the level of sensitiveness either by increase (supersensitization) or decrease (approach to desensitization) by previous tests; (5) the possible establishment of sensitiveness by injection of tuberculin and (6) native fluctuations in sensitiveness without regard to demonstrable changes in underlying disease.

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] In this connection it is interesting to comment on the fact that Nalbant (1) failed to find that deleterious effects followed the occurrence of intercurrent diseases in tuberculous children in a sanatorium.

Two reviews on subjects closely related to this one have appeared in the last few years. These reports, one by Tytler (2) and one by Hart (3), have both presented considerable pertinent data from the literature. Schwartz and Heise (4) tested patients with tuberculin on admission to the sanatorium and retested them later with the same dose to detect changes in sensitiveness, if any. They found that one-half of 23 patients with extensive tuberculosis showed a decrease, as indicated by the extent of reaction, and concluded that no correlation could be demonstrated between the degree of tuberculin sensitiveness and amount of disease. These workers dealt with adults. However, the work of Johnston, Howard and Maroney (5) seemed to indicate that, in children with tuberculosis of the lungs, sensitiveness to tuberculin tends to increase in degree until lymph node enlargement reaches its height and the pulmonary lesion begins to undergo resolution. And Lobban (6), upon repeating tuberculin tests on patients whose disease was improving, noted a tendency toward increase in sensitiveness and vice versa in those patients who were doing badly.

Despite the array of conflicting data and complicating features that attend such studies, we began our work in the hope that testing at intervals might yield information of prognostic value when done in tuberculous patients whose course was under prolonged clinical, X-ray and laboratory observation. We endeavored to obtain facts which would (possibly) enable us to: (1) anticipate prognosis (does cutaneous reaction drift constantly in one direction?); (2) predict change in the course of the disease (does the reaction fluctuate consistently before or at the time of change in the course of the disease?); (3) obtain indications for therapy; (4) get correlation between symptoms, signs, X-ray and laboratory examinations and the state of tuberculin sensitiveness; (5) determine, if possible, the degree and changes in sensitiveness in the course of disease which is predominantly fibrotic, exudative or mixed, insofar as these may be determined accurately; (6) learn the possible trend and fluctuation of sensitiveness in cases which proceed to healing, in those that are stationary and in those that are progressive; (7) compare trends and fluctuations, if any, in tuberculosis of so-called childhood and adult types, and in those individuals in whom the disease merges from the childhood type to the adult type; (8) observe whether exacerbation of disease or change of bacilli in sputum (positive to negative or vice versa) is associated with change in sensitiveness.

PROCEDURE

Careful records were made of the clinical, X-ray and laboratory status of the patients each time the tests were performed, the intervals of which varied from three weeks to three months. All records were eliminated from final consideration if at least three sets of tests had not been done or if complete data lacked in any particular. The final analysis was based upon the records of 179 patients.

It was hoped that we might determine the smallest dose which would elicit a reaction in a given individual and establish that as a standard dose for him and, in subsequent tests, use this standard dose to determine whether the degree of sensitiveness of that individual had changed. But potency varied considerably in very weak dilutions, even in freshly prepared ones. Therefore, dilutions were used that were somewhat stronger than the greatest to which the individual would just react, and the size and intensity of the reacting area became criteria of changing sensitiveness. If the reaction were greater to a given test than to a previous test, retest was done promptly with the next weaker dilution; if the test failed to elicit a reaction, retest followed with the next stronger dilution. Thus the response to varying dilutions and the degree of the response were depended upon to indicate changes in the sensitiveness.

A description has been given (7) of the different types of tuberculin used and the manner of evaluating potency of one with respect to another. Suffice it to say here that Seibert's ultrafiltrate, trichloracetic acid precipitate tuberculin (T.P.T.), T.P.T. in tablet form and Old Tuberculin were used at different stages of the study. Usually Old Tuberculin was applied to one arm and one or another of the newer products was applied simultaneously to the other. All dilutions were prepared on the day on which they were applied. Tests were made in patients in all stages of pulmonary tuberculosis and in numerous people with nonpulmonary tuberculosis. They were repeated at intervals for at least as long as six and often for as long as twelve months and even two years. They were made systematically in the skin of the forearm so that sites of previous injections were avoided.

ANALYSIS OF DATA

With this number of patients, each of whom had many tests over periods ranging from a few months to two years, it was felt that evidence would appear which would point to certain relationships between tuber-

culin sensitiveness and the course of the disease in the given individual. On the whole the results indicated much fluctuation in sensitiveness with but little coördination between tuberculin sensitiveness and the several factors enumerated above. The following are the essential data in the study.

In grouping these results two approaches from a purely objective handling of the data could be made; the first of these would be to group all the patients in whom decreasing sensitiveness was found and all those in whom increasing sensitiveness was found and then see if the patients demonstrating one of these states had something in common that the other group did not, or vice versa. Attempts in this direction failed singularly. There seemed to be no regularity at all as to the type of case or progress of the disease in the cases which fell under these two headings.

The second approach was to group the patients according to the course of the disease, paying particular attention to the X-ray findings and then determine if these groups showed any similarity in tuberculin response. Those patients in whom definite changes could be seen were selected as being most promising of definite results, and they were grouped into four types; first, those healing by fibrosis; second, those healing by resolution; third, those healing by resolution and fibrosis; and fourth, those showing progressive, destructive lesions.

The data germane to this classification are shown in table 1. One hundred fifty-eight patients grouped in this manner all showed definite changes under the four headings as indicated. Those in whom no especial change could be noted were not used in this tabulation. Some difference may be noted between the reaction in those in whom recovery was taking place and those in whom the disease was progressive. The progressive group had decreasing sensitiveness in 55.5 per cent, whereas the recovering group had decreasing sensitiveness in only 21.1 per cent. In the improving group those with increasing sensitiveness were more than twice as numerous as those among the progressive group (35.6 per cent as compared with 16.6 per cent). However, such a large percentage of individuals showed no change in sensitiveness, 43.3 per cent in the improving group and 27.8 per cent in the progressing group, that, after all, it seems inadvisable to conclude that decrease in sensitiveness suggests progressive disease, and even less does it appear that increase in sensitiveness indicates a favorable course.

Further division of the favorable group into the various types of healing did not result in any striking difference as to sensitiveness. Those healing by fibrosis, by resolution, and by a mixture of both proc-

esses all showed a very large number with no alteration in sensitiveness during the period of observation. Therefore, it appears that healing in any of these three manners is not accompanied by any characteristic change in sensitiveness.

It has been reported that children who develop first infection with tubercle bacilli show a rather definite response to tuberculin that is characterized by rapidly increasing sensitiveness followed by decreasing sensitiveness (Johnston, *et al.* (5)). It does not appear from our study, however, that any definite trend continues during the healing process. A small group of twenty-one children with childhood-type lesions, which

TABLE 1*

SENSITIVENESS	IMPROVING								PROGRESSIVE		TOTAL NUMBER
	Fibrosis		Resolution		Mixed		Total				
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
Increasing	8	28.5	26	38.8	3	33.3	37	35.6	9	16.6	46
Decreasing	8	28.5	13	19.4	1	11.1	22	21.1	30	55.5	52
Stationary	12	42.8	28	41.8	5	55.6	45	43.3	15	27.8	60
Total	28	99.8	67	100.0	9	100.0	104	100.0	54	99.9	158

* Data are described in the text.

TABLE 2*

Children in whom healing by resolution occurred

INCREASED SENSITIVENESS		DECREASED SENSITIVENESS		STATIONARY		TOTAL NUMBER
Number	Per cent	Number	Per cent	Number	Per cent	
9	43	4	19	8	38	21

* Data are described in the text.

underwent healing by resolution during the period of serial testing, showed no uniform trend, as may be observed in table 2.

No patient in whom a definite diagnosis of tuberculosis was made failed to react to tuberculin. Furthermore, no individual who reacted positively became negative during the observation: even though sensitiveness decreased, it did not disappear.

Questions concerning variation in sensitiveness and in the factors enumerated above which may enhance or lower this state require no extended discussion. This is true particularly because, in each group of these patients, considerable numbers deviated in one direction while at

times almost equal numbers deviated in the other. In other words, the results point to no unequivocal underlying or fundamental trends of sensitiveness in the presence of healing or progression.

The question may be raised as to whether the repeated tuberculin tests may have modified the patients' later reactions. In this respect it need only be pointed out that no constant increase or decrease in sensitiveness associated itself with the increase in the number of tests.

SUMMARY AND CONCLUSIONS

A prolonged series of observations on tuberculous patients in whom tuberculin tests have been repeated a number of times has led to the general conclusion that tuberculin sensitiveness fluctuates variously but not closely in accord with changes in the patient's condition. In patients who were improving, sensitiveness increased in 35.6 per cent, decreased in 21.1 per cent and remained stationary in 43.3 per cent. In patients whose disease was progressing, these figures were 16.6 per cent, 55.5 per cent and 27.8 per cent, respectively. The only definitely objective trend seen is in the fact that sensitiveness decreased in 21.1 per cent of improving and in 55.5 per cent of failing patients. Although this difference in percentage may be considerable, the fact should be noted that many exceptions occurred and it is thought that this trend is interesting rather than significant.

A considerable number of patients varied greatly in the degree to which they reacted to tuberculin; the variation at times representing an increase and at times a decrease in sensitiveness and practically always without evidence of associated clinical, roentgenological or laboratory change. These points were not included in the tabulation.

From the data at hand definite conclusions cannot be drawn as to association between tuberculin sensitiveness and prognosis in tuberculosis. In fact, the evidence would indicate that no such relationship exists.

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THE APPLICATION OF THE NEWER PURIFIED TUBERCULIN PRODUCTS BY THE PIRQUET METHOD

ARTHUR H. STEELE[1] AND HENRY STUART WILLIS[2]

It has long been the desire of those who work with tuberculin to possess a product which is exactly measurable and which contains few or no ingredients other than the specific protein of the tubercle bacillus. Seibert's admirable work has, as is well known, yielded two products (MA-100 or T.P.T., and P.P.D.) which have now had extensive clinical application. In these products, and especially in the latter, it appears that this hope has approximated realization.

Although these products have had wide clinical application, all of it has been by the intracutaneous method. They have not been applied by the Pirquet technique, doubtless for the reason that the method is inexact in that the degree of absorption by the skin cannot be evaluated and thus the dose cannot be determined. However, data on the Pirquet test from many sources compare rather closely and indicate a fairly constant ratio between the tuberculin test when applied by this and by the Mantoux technique, the Pirquet method yielding about 15 per cent fewer reactions.

Those who have applied tuberculin on a comprehensive scale have encountered varying degrees of parental resistance to the test, but they have found much less resistance to a "scratch" test than to an "injection" test. Now that these purified products are available, the question rather naturally arises as to whether they may be applied by the Pirquet method where circumstances may make this desirable. It seems well to have recourse to such a combination of material and method if needed. We prefer the Mantoux procedure but believe that at times the Pirquet test may and should be employed. The materials used in this work were Old Tuberculin, Purified Protein Derivative, and Trichloracetic Precipitate Tuberculin. The two latter were furnished by Dr. Florence Seibert, of the Henry Phipps Institute, and Dr. L. T. Clark, of Parke, Davis & Co. Certain lots of these products came in tablet form and others in solution which contained 10 mgm. per cc.

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The work consists of a comparative study of the incidence of reaction when Old Tuberculin and P.P.D. and T.P.T. in varying strengths are applied to children simultaneously by the Pirquet method. A small group of nonreactors were tested by the Mantoux method. Where tablets were used, the diluent was physiological salt solution, fifty per cent glycerine or a buffered glycerine vehicle. The tuberculin was allowed to stand on the scratched area for five minutes, when the excess was removed with sterile cotton. In instances in which the salt solution diluent evaporated before the five minute contact period had elapsed, application of another drop was made. The children were resident in a school for the mentally retarded and were all clinically nontuberculous.

This report presents the results of tests on 540 children. Each child received two tests on one arm and one test and a traumatic control on the other. All were made simultaneously.[3] The test areas were examined 24 and again 48 hours after the tuberculin had been applied. The ages ranged from 9 to 16 years. In each series of tests undiluted Old Tuberculin was compared with P.P.D. and T.P.T.; the latter were used in dilutions that varied from 0.05 mgm. per cc. to 10 mgm. per cc. The results are shown in table 1.

From that table it will be seen that 223 of the children, ranging in age from 9 to 16 years, were tested with undiluted Old Tuberculin, with P.P.D. 0.05 mgm. per cc. and T.P.T. 0.1 mgm. per cc. Of those, 39 (17.0 per cent) reacted to Old Tuberculin; 2 (0.89 per cent) to P.P.D., and 7 (3.1 per cent) to T.P.T.

Eighty-one children from 12 to 15 years old received Old Tuberculin in undiluted strength and P.P.D. and T.P.T. each in a strength of 1 mgm. per cc. Of these children, 12 (14.8 per cent) reacted to Old Tuberculin, 7 (8.6 per cent) to P.P.D., and 6 (7.4 per cent) to T.P.T.

In the next group the concentration of P.P.D. and T.P.T. was increased to 10 mgm. per cc. Two hundred twenty-six children between 10 and 15 years of age were tested in the manner just described for the other groups, with the result that Old Tuberculin elicited reaction in 34, or 15.1 per cent; P.P.D. (10 mgm. per cc.) brought out reaction in 28, or 12.4 per cent; and T.P.T. (10 mgm. per cc.) caused 30, or 13.3 per cent, to react.

Sixty-seven unselected children, who belonged to the group of 226 and who failed to react to any of the three types of tuberculin, were

[3] An ordinary stylette made for obtaining blood from the finger was used after the point had been made blunt and round.

tested by the Mantoux method with 0.1 cc. each of Old Tuberculin 1:1000, P.P.D. 0.05 mgm. per cc., and T.P.T. 0.01 mgm. per cc. Four (5.97 per cent) reacted to Old Tuberculin and to P.P.D., and 13 (19.4 per cent) to T.P.T. These data are shown in table 2.

From this it is clear that P.P.D. or T.P.T., if used by the Pirquet method in a concentration of 10 mgm. per cc., elicits reaction in 12 or

TABLE 1

Response to Pirquet test

NUMBER	AGE GROUP	REACTORS					
		O.T. (undiluted)		P.P.D. (0.05 mgm. per cc.)		T.P.T. (0.1 mgm. per cc.)	
		number	*per cent*	*number*	*per cent*	*number*	*per cent*
223	9–16*	39	17.0	2	0.89	7	3.1
		O.T. (undiluted)		P.P.D. (1 mgm. per cc.)		T.P.T. (1 mgm. per cc.)	
		number	*per cent*	*number*	*per cent*	*number*	*per cent*
81	12–15	12	14.8	7	8.6	6	7.4
		O. T. (undiluted)		P.P.D. (10 mgm. per cc.)		T.P.T. (10 mgm. per cc.)	
		number	*per cent*	*number*	*per cent*	*number*	*per cent*
226	10–15	34	15.1	28	12.4	30	13.3

* Eighteen of those in this group were over 16 years of age. Five of them were reactors.

TABLE 2

Response to Mantoux test in Pirquet negative children

NUMBER	AGE GROUP	REACTORS					
		O.T. (1–1000)		P.P.D. (0.05 mgm. per cc.)		T.P.T. (0.01 mgm. per cc.)	
		number	*per cent*	*number*	*per cent*	*number*	*per cent*
67	10–15	4	5.97	4	5.97	13	19.4

13 per cent of children as compared with 14 or 15 per cent of reactors to Old Tuberculin. On the basis of these observations it is believed that those who find the Pirquet method either necessary or preferable may employ it with these newer, purified tuberculin products with the expectancy of results that are comparable to those from the use of Old Tuberculin.

CONCLUSIONS

Although the intracutaneous method is preferable to the "scratch" test (Pirquet), there are circumstances, such as parental objection to "injections," when the Pirquet manoeuvre may be utilized advantageously.

It has been shown that the newer, purified tuberculin products, T.P.T. and P.P.D., may be used satisfactorily by the Pirquet method. When used in a strength of 10 mgm. per cc., these products elicit reaction in approximately the same incidence as Old Tuberculin does.

THE DIAGNOSTIC APPLICATION OF HIGH DOSES OF TUBERCULIN[1]

M. PARETZKY

In spite of the fact that the intracutaneous tuberculin (Mantoux) test has been extensively used during recent years, its diagnostic value is still questioned in some quarters. The customary objection is that certain cases which yield a negative reaction to the routinely applied doses (0.01 mgm. and 0.1 mgm. of Old Tuberculin) clinically prove to be cases of active tuberculosis.

While using the tuberculin test we must not forget that it is directly a test for tuberculoallergy; and only indirectly, inasmuch as tuberculoallergy cannot exist in the absence of tuberculous infection, is it a test for the presence of tuberculous infection.

Many varied factors influence tuberculoallergy. According to Krause (1) the degree of tuberculoallergy depends on the original dosage of infection and the time since infection. Among the factors which influence the degree of the reaction Krause (1) has cited as the most important the degree of allergy and the dosage of the applied antigen. As other factors he has mentioned the amount and character of skin pigmentation and hereditary factors.

Pilcher (2) has suggested that the degree of reaction depends to a certain extent upon the state of the circulation in the skin and subcutaneous tissues. According to Corper (3) this observation by Pilcher was confirmed by Reichel and Milbradt who have also expressed the opinion that the reaction was accentuated in individuals with tender, soft skins and diminished in those with dry, hard or brittle skins.

Burhans (4) has cited a number of workers—as Hamburger and Preyer, Schimpenkötter—who have reported seasonal variations in allergy. It is also known that many acute and chronic pathological conditions influence the reaction to a marked degree, as do certain drugs.

It is evident that all these factors can produce great variations in the degree of the reaction not only in different individuals but also in the same individual at different times.

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It is obvious that in order to meet all possibilities resulting from the described shifting of the reactive ability of the skin, the test also must be mobile. A number of authors have suggested the use of progressively increasing doses of tuberculin if the initial lower doses prove to be negative. To mention only a few, Burhans (4) has advocated the application in such instances of consecutive doses of 1.0 and 10.0 mgm. Lichtenstein (5) has used even higher doses of tuberculin, in dilutions up to and including 1 to 1.

A considerable degree of diagnostic misunderstanding is possible if sufficiently high doses of tuberculin are not used. Thus, Hetherington and coworkers (6) have reported that, out of 82 children negative to 1.0 mgm. of Old Tuberculin, seven, or 8.5 per cent, showed tuberculous pulmonary nodules, and three, or 3.7 per cent, showed tuberculous

TABLE 1

The readings of the intracutaneous tuberculin (Mantoux) test in 334 cases of adult active pulmonary tuberculosis

THE RESULTS OF TUBERCULIN TESTING	NUMBER OF CASES	PER CENT
Positive to 0.1 mgm. or to lower doses	316	94.61
Negative to 0.1 mgm. Higher doses not applied	2	0.59
Positive to 1.0 mgm.	8	2.39
Positive to 10.0 mgm.	4	1.19
Negative to 10.0 mgm.	4	1.19
Total	334	99.97

tracheobronchial lymph nodes. It is not impossible that at least some of these children would react to 10.0 mgm. of Old Tuberculin if this dose would be applied. However, other authors have reported a much lower margin of a possible diagnostic error. Thus, Tattersall (7) has found that a negative reaction to 0.1 mgm. of Old Tuberculin excludes the presence of tuberculosis with a margin of error from 2 to 4 per cent. According to Lichtenstein (5), Hart has established approximately the same margin of error.

We have had an opportunity to collect data on 334 cases of proved active pulmonary tuberculosis in adults observed by us in the chest clinics of the Los Angeles County Health Department during the period of approximately two years, from 1934 to 1936. These data are presented in table 1.

As initial dose we have routinely used 0.1 mgm. of Old Tuberculin;

in cases with negative reactions to this dose 1.0 mgm. was applied; if again a negative reaction followed, 10.0 mgm. was applied. The intracutaneous (Mantoux) method was used. Commercial Old Tuberculin, a product of the same firm, has been used throughout this series.

Brief histories of three of the four cases proved to be negative to 10.0 mgm. were reported by us in a previous publication (8). If we exclude this group of cases, we shall see that 98.19 per cent of the collected cases have yielded a positive reaction to one of the applied doses of Old Tuberculin. It is evident that the technique used has given an exceedingly high percentage of positive reactors among our cases of active pulmonary tuberculosis. If we exclude the two cases which were negative to 0.1 mgm. but were not tested with higher doses, we shall find that in our series 3.58 per cent of the total were negative to 0.1 mgm., which corresponds very closely to the figures reported by Hart (5) and Tattersall (7).

THE DIAGNOSIS OF CLINICAL TUBERCULOSIS

We have encountered a great variety of tuberculous lesions among the cases negative to 0.1 mgm. of Old Tuberculin. Nodular infiltrations, fibrocaseous lesions, caseous consolidations, cavitations and different degrees of fibrosis were observed. In some of the cases the positive tuberculin reaction was a factor of great importance in establishing the diagnosis of tuberculous disease. As an illustration we shall report briefly one of these cases.

Case 1: White, male, age 46, had symptoms of an active pulmonary disease. Six sputum specimens were negative for acid-fast bacilli on direct smear. Three X-ray films taken over a period of seven months displayed essentially the same findings of a massive density occupying a large portion of the right upper lobe and a small area of infiltration in the left apex. These findings were reported as suggestive rather of a neoplasm than of tuberculosis. There was a one-plus reaction to 10.0 mgm. of Old Tuberculin, negative reactions to lower doses. The clinical diagnosis of active tuberculosis made by us was confirmed later by several sputum tests positive for acid-fast bacilli. The X-ray aspect changed later; there was a downward spreading, and a central rarefaction appeared in the massive consolidation. Five months after the first application the tuberculin reaction was positive to 0.001 mgm.

The diagnosis of nonpulmonary tuberculosis can be considerably aided by the application of high doses of tuberculin as is evident from one of the cases of this type seen by us.

Case 2: Mexican, female, age 3, with a history of exposure to a case of active pulmonary tuberculosis. She had occasional elevations of temperature; the cervical lymph nodes were slightly enlarged; physical findings over the chest were essentially negative. The tuberculin reaction was consistently negative to several progressively increased doses of Old Tuberculin and positive to 10.0 mgm. only. The X-ray revealed a considerable shadowing at the right hilum. Six months later a slight decrease of the above shadowing and a beginning calcification were demonstrated radiologically.

Arrested tuberculosis can be diagnosed in some cases with the assistance of a negative reaction to high doses of tuberculin.

Case 3: White, female, age 22. She has had loss of weight, loss of strength, slight dyspnoea, hoarseness, cough, mucous expectoration. Physical examinations repeatedly revealed sonorous and sibilant râles over both lungs. X-ray films have shown a slight nodular and linear type of infiltration in the left apex. The peribronchial markings in the left base were unusually heavy. Ten months later considerable fibrosis was evident in the left apex, also some clearing of the peribronchial markings in the left base. Sputum was persistently negative on direct smear, on culture and on animal inoculation. About six years before admission to our clinic the blood Wassermann test was four-plus on two consecutive examinations. The patient had a prolonged course of specific treatment. The Wassermann test was negative shortly after admission to our clinic. A possibility that the lesion in the left base could be of syphilitic aetiology was considered, but no evidence of pulmonary syphilis was elicited on bronchoscopy. Series of tuberculin tests including the dose of 10.0 mgm. were negative over a period of over one year. The case was diagnosed as one of minimal pulmonary tuberculosis, arrested.

THE DIAGNOSIS OF NONTUBERCULOUS CONDITIONS

The great diagnostic value of negative tuberculin reactions has been universally recognized. It seems to us that, in view of the marked variability of the tuberculin reaction, large doses must be applied to assure a complete reliability. In our opinion a negative reaction to 10.0 mgm. of Old Tuberculin can, with very few exceptions, be reasonably accepted as evidence against the presence of tuberculous infection. We have encountered several instances in which a negative reaction to this dose has helped to exclude tuberculosis in cases otherwise suggestive of this disease.

Case 4: White, male, age 34, with a history of a previous exposure to tuberculous infection. He had an attack of pneumonia, after which he had some night

sweats and cough for about one week. He was examined in a private clinic where his sputum was reported positive for acid-fast bacilli, and a diagnosis of active tuberculosis was made. On physical examination by us there were no abnormal pulmonary findings. A double murmur was heard over the pulmonary artery. The patient had negative tuberculin reactions to four consecutive doses up to and including 10.0 mgm. The sputum was negative on direct smears and culturally. The X-ray film was also negative for tuberculosis.

Case 5: White, female, age 22, with a history of exposure to a tuberculous cousin. She had chills, fever, night sweats, poor appetite, indigestion, pains in the chest, cough, blood-streaked expectoration, dyspnoea and hoarseness. The physical findings over the chest were negative. Tuberculin tests, including the dose of 10.0 mgm., were negative. Six direct smears of the sputum and a guinea-pig inoculation were negative for acid-fast bacilli. An X-ray film was negative for tuberculosis. The symptoms cleared up within seven weeks after the examination.

In cases with evidence of some chest ailment a definite exclusion of tuberculous disease is an important procedure leading to a correct diagnosis. Negative reactions to high doses of tuberculin are undoubtedly very helpful in such instances. They were observed by us in a number of cases of various pathological conditions.

Case 6: White, male, age 3. Prior to admission he had influenza complicated by bronchopneumonia. Three months later he had measles, after which he had fever, loss of weight, loss of strength and cough for about three weeks. An X-ray picture of the chest was taken by the family physician after which the patient was referred to us with a diagnosis of tuberculosis. The chest findings on physical examination by us were negative. The fever subsided within a week. Tuberculin tests, including the dose of 10.0 mgm., were negative. An X-ray film revealed a small area of density in the right base, with enlarged lymph nodes. These findings were reported by the roentgenologist as suggestive of a primary parenchymal tuberculous lesion, but the possibility of bronchopneumonia was also indicated. We made a clinical diagnosis of bronchopneumonia. Another X-ray film taken five weeks later showed a complete clearing of the lesion.

Case 7: White, female, age 3 on admission. She attended the chest clinic for over five years. There were fluctuations in weight over this period of time with alternating gains and losses. Occasional "colds" without fever have been reported. Physical findings on repeated reëxaminations displayed occasional

moist coarse râles over both bases, intermittently increasing and decreasing to the point of complete disappearance. Many X-ray films taken during this period of time showed a cavitation in the right midinfraclavicular area, definite cavitations in the bases of both lungs, one in each, also several smaller ones scattered through both lung fields. There was at times a hazy parenchymatous infiltration in either lung. Several of the small cavities disappeared in the course of time. At times some of the cavities displayed a distinct fluid level. The constant localization of one of the cavities in the right midinfraclavicular area was considered as a rather rare finding for a bronchiectatic cavity in a child of this age and the described closing of some other cavities was suggestive of tuberculosis. Other findings pointed to a diagnosis of bronchiectasis. On the whole the roentgenological findings were inconclusive for either of the conditions. Several tuberculin tests with different doses, including 10.0 mgm., were negative. The sputum was persistently negative on numerous direct smears, on culture and on guinea-pig inoculation. These facts combined with the absence of reactions to high doses of tuberculin have, in our opinion, definitely excluded tuberculosis, establishing a diagnosis of bronchiectasis.

The following case was one of pneumonoconiosis. The presence of tuberculous infection was for a while excluded by negative tuberculin tests. We shall discuss some details of this case in a later part of this paper.

Case 8: White, male, age 63, a gold-miner for about 30 years. On physical examination there was diminished resonance over both supraspinate and upper interscapular areas. Sonorous and sibilant râles were constantly heard scattered over both lungs. The heart tones were muffled. Roentgenologically there was seen a very dense shadow at the hilum and in perihilar areas in both lungs fading out toward the bases and apices. Both domes of the diaphragm were flattened, probably due to emphysema. The heart and the mediastinum were slightly displaced to the right. Several direct smears and a culture were negative for acid-fast bacilli. The tuberculin readings on initial testings were negative to all doses including 10.0 mgm., but two tests with 0.1 mgm. made approximately one year and one and one-half years later were positive.

Case 9: Mexican, male, age 3 on admission. He has attended the clinic for approximately six years during which period of time he has had several acute attacks accompanied by high fever, night sweats, loss of weight, dyspnoea, cough, purulent expectoration, sometimes vomiting and acute abdominal pains. The tonsils and the cervical lymph nodes were markedly enlarged. On physical examinations during these attacks numerous moist, large and medium

size râles were heard over both lungs. The white blood-cell count on one such occasion was 29,000. The patient was hospitalized several times. The sputum was repeatedly negative on direct smears. Several X-ray pictures, taken over a period of almost six years during and between the described attacks, presented essentially the same findings of marked uncalcified shadows in both hilar areas which at times and especially towards the end of the period of attendance showed a tendency to partial clearing. No infiltrations were noted in the peripheral portions of the lungs. A clinical diagnosis of pulmonary abscess was made in this case. However, roentgenologically the case was reported at the beginning of the period of attendance as suggestive of tracheobronchial tuberculosis. Bronchoscopy with lipiodol visualization established a diagnosis of bronchiectasis.

Case 10: Mexican, male, age 40. He had a rib resection on account of a right-sided empyema. He was diagnosed at that time at the hospital in which he was operated upon as having pulmonary tuberculosis. He was seen in the chest clinic three years later. Physical examination revealed diminished resonance, diminishing breathing over the right base, pleural friction over most of the right lung, especially dorsally. An X-ray film showed a slight increase of radiability in the right costophrenic angle which, although suggestive of a cavitation, was considered as probably due to adhesions so arranged as to simulate a cavity. A tuberculin test with 0.1 mgm. was positive. Six months later the patient was seen again, with considerable loss of weight and cough. Five consecutive tuberculin tests with doses starting from 0.001 mgm. and ending with 10.0 mgm. were negative. The test was repeated ten months later with a dose of 1.0 mgm. and was again negative. The patient was assured that he was not afflicted with an active tuberculous disease. He is well and is working at present.

Case 11: White, female, age 22. She complained of cough, expectoration, slight chest pains. Within three years she had about fifty haemorrhages of varying frequency and quantities. She had several "colds" during which cough and expectoration were usually worse. Her temperature occasionally rose to 99.4°F. There were some fluctuations in weight with a marked general tendency to loss. Repeated physical examinations revealed a slightly diminished resonance over the right apex. The cardiac findings have never revealed any abnormality. Series of X-ray films taken over a period of two years have shown a slight enlargement of the right hilum lymph nodes, a large calcified nodule in the right perihilar area surrounded by a slight infiltration which at times made the impression of not being entirely healed. The blood count and the Wassermann test did not indicate anything abnormal. A number of sputum tests were negative on direct smears, on culture and on

guinea-pig inoculation. Bronchoscopy revealed a small amount of blood exuding from a tiny bronchial orifice on the posterior wall of the left main stem, apparently the branch supplying the upper posterior portion of the left lower lobe. There was nothing in the region of the orifice to suggest the aetiology of the haemorrhage. For about two years serial tuberculin tests were negative to all doses except to 10.0 mgm. At the end of the period of attendance this dose also gave a negative reaction. Some marked symptoms of cardiac decompensation have been noted at the end of the period of attendance. An electrocardiographic tracing has been reported as suggestive of a mitral valve lesion with a slight auricular hypertrophy.

Case 12: White, male, age 8. He had night sweats, fever, loss of strength, and some skin eruption resembling chicken pox. The cervical lymph nodes were enlarged. The physical findings over the lungs were essentially negative. Tuberculin tests with 0.1 mgm. and 1.0 mgm. were negative. The blood serum was positive for *Brucella Melitensis* in a dilution of 1:800.

Case 13: White, male, age 8. He complained of loss of weight, loss of strength, slight afternoon fever, dry cough, occasional dyspnoea. The physical findings over the chest were repeatedly negative. An X-ray film revealed a slight enlargement of the hilum lymph nodes bilaterally. The peribronchial markings were quite heavy in both perihilar regions. These findings were considered as suggestive of active tracheobronchial tuberculosis. Two series of tuberculin tests, including the doses of 10.0 mgm., made over a period of six months, were negative. An X-ray film, taken six months after the first one, was reported by the roentgenologist as not indicating a tuberculous involvement. The case was diagnosed as nontuberculous tracheobronchial adenitis.

Case 14: White, male, age 1 year and 3 months. He was admitted to the clinic without symptoms suggestive of pulmonary disease. He has been fed for a long time on raw milk from cows suspected of being tuberculous. The chest findings on physical examination were negative. Left cervical lymph nodes were markedly inflamed, with an abscess which was lanced in a hospital, but there was no draining on admission. The chest X-ray films were essentially negative. Tuberculin tests were negative with all doses including 10.0 mgm. The case was diagnosed as nontuberculous cervical adenitis.

DISCUSSION

In many instances when large numbers of persons are examined for tuberculosis there is a working rule to X-ray only positive tuberculin reactors. In our series of cases of active pulmonary tuberculosis, twelve patients, or 3.58 per cent of the total, had a negative reaction to 0.1

mgm. of Old Tuberculin, the dose which is routinely applied on first examination by most workers. This is rather a large margin of error. On the other hand, only four patients, or 1.19 per cent of the total, were negative to all higher doses of tuberculin, including 10.0 mgm. It seems that, in view of this low margin of a possible error, applications of gradually increasing doses of tuberculin, including 10.0 mgm., to persistently negative reactors would be a much safer diagnostic procedure. We believe that this technique may be of practical value. Thus, in the endeavor to reduce the high costs of roentgenological examinations, it has been our routine not to refer for X-rays negative reactors to 10.0 mgm., provided there were no other clinical indications for radiography. A reliable negative tuberculin reaction is of great diagnostic value. We have cited a number of different pathological conditions encountered among patients negative to 10.0 mgm. of Old Tuberculin. By far not all collected cases have been reported here. We have had in most instances several cases of each type described; we have also had in this series a case of primary pulmonary carcinoma with a negative reaction to 10.0 mgm. of Old Tuberculin. In the cases in which tuberculous disease could be reliably ruled out on the basis of a negative reaction to 10.0 mgm., a saving of a considerable amount of diagnostic work and of time could be accomplished, a consideration of importance on some occasions as, for instance, in cases of suspected pulmonary carcinoma, in which emergency surgery would be indicated. Of course, it must be remembered that, due to the widespread prevalence of tuberculous infection, many individuals though clinically nontuberculous are nevertheless positive tuberculin reactors. Furthermore, many cases of active tuberculosis could be diagnosed even without the use of the tuberculin test. Therefore, the described technique of tuberculin testing could be of a diagnostic value only in a limited number of cases. But just these limited cases usually present certain diagnostic difficulties as some of the cases reported here did. Every experienced clinician knows that every diagnostic clue may be of practical significance in cases of this type.

We do not advocate a wholesale use of the described technique for all negative tuberculin reactors. As with many other important diagnostic tests, the application of high doses of tuberculin should depend on the clinical judgment of the examining physician. A definite history of exposure to tuberculous infection and symptoms and signs suggestive of tuberculosis should be considered as the indications for its use.

Some secondary issues which have attracted our attention during the study of the subject are perhaps sufficiently interesting to be briefly discussed. In one instance (case 6) the patient, a child of three, had measles approximately six weeks prior to the last negative test with a dose of 10.0 mgm. According to Pilcher (2), in measles the positive tuberculin reaction is lost from two to four days after the appearance of the rash and is restored on the twenty-first day. We felt that in this case the period of restoration of the positive tuberculin reaction, if such had existed previously, had already been reached. Furthermore, there was no known exposure to tuberculous infection in the household which at this age would make the implantation of tuberculous infection in this child rather improbable. These considerations have influenced us in accepting the negative reaction to 10.0 mgm. of Old Tuberculin as definitely ruling out tuberculosis. The diagnosis of bronchopneumonia made clinically was later confirmed by X-ray.

Recent studies of silicotuberculosis made in this country by Gardner and others indicate very convincingly that as a rule silicosis precedes and is a predisposing factor for the development of tuberculous disease. This conception was disputed by some European workers, and especially by Rist (9). According to them different morbid changes in the lungs, including those produced by active tuberculosis infection, would lead to silicosis after a prolonged exposure to silica dust. In other words, tuberculosis, coexisting with silicosis would, according to this concept, precede silicosis. In one of our patients (case 8) with a definite diagnosis of pneumonoconiosis a negative reaction to all doses of Old Tuberculin, including 10.0 mgm., has definitely excluded the existence of tuberculous infection. Two other applications of 0.1 mgm., one and one-and-a-half years later respectively, gave positive reactions, thus indicating the introduction of tuberculous infection. At present we have no further data on this case which would enable us to state whether clinical tuberculosis has actually developed. But on the basis of the above facts it seems logical to assume that in our case the implantation of tuberculous infection was chronologically secondary to silicosis.

In two instances there was a record of previously existing positive tuberculin reactions, in one (case 10) to a dose of 0.1 mgm., in another (case 11) to a dose of 10.0 mgm. of Old Tuberculin. Barring possible mistakes in the initial skin test readings, these two instances could be interpreted as characteristic for the process of disappearance of specific skin hypersensitiveness which is known to take place in certain cases.

In case 14 there was a history suggestive of a possible introduction of bovine infection through raw milk; cervical lymphadenitis was present. All consecutive doses of human tuberculin, including 10.0 mgm., yielded negative reactions. It would be important to make clear whether negative reactions to high doses of human tuberculin could exclude bovine tuberculosis. In the days of Detré it was thought that tests with different types of tuberculin could definitely differentiate between the bovine and the human types of tuberculous infection. After the change of the accepted technique from the cutaneous (Detré) method to the intracutaneous (Mantoux), this concept was supported for some time by some workers, among others by Downing and Higgins (10). Later a change of opinion took place. According to Dolgopol (11), Sorrentino has confirmed the report of Hermann that at first the specific reaction appears with the tuberculin of the infecting type and that later in the disease "group reactions" with other tuberculins also appear. However, several authors, as for instance Tisdall and Brown (12), have reported that in the series of cases tested by them there was no essential difference in reactions to different types of tuberculin. According to Tisdall and Brown (12) the fact that positive reactions have been obtained with one tuberculin and negative reactions with the other, is due to a difference in the amount or potency of the tuberculin used. An increase of dosage or potency may increase the reaction and may produce a positive reaction where previously it was negative with a lower dose or a lower potency. According to these authors Calmette has expressed essentially the same opinion as early as 1920.

This opinion, based on clinical observations, was confirmed by Lewis and Seibert (13) on experimental animals. The authors found that a definite antigenic relationship exists between the three types of tuberculoproteins, to the extent that guinea pigs sensitized to one tuberculin gave anaphylactic reactions to others, except the proteins of the timothy-grass bacillus. On the basis of all these facts, one may safely assume that a negative reaction to high doses of human tuberculin will exclude the presence of bovine infection.

SUMMARY AND CONCLUSIONS

1. Data have been presented justifying the diagnostic application of high doses of tuberculin, including 10.0 mgm., to persistently negative reactors with a history and findings suggestive of chest diseases.

2. A number of tuberculous and nontuberculous cases have been briefly

reported in which this technique has helped in establishing the correct diagnosis.

3. Some secondary issues encountered during the study of the subject have been briefly discussed.

We wish to express our appreciation of the encouragement of research work in the Tuberculosis Division of the Los Angeles County Health Department by Dr. J. L. Pomeroy, County Health Officer, and Dr. P. K. Telford, Chief of the Tuberculosis Division. We wish to thank Dr. M. L. Pindell, roentgenologist, for his able X-ray interpretations.

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A NEW ADMINISTRATIVE TECHNIQUE IN TUBERCULOSIS CASE-FINDING[1,2]

BRUCE H. DOUGLAS AND HENRY F. VAUGHAN

Case-finding in tuberculosis is recognized by everyone engaged in the attempt to control this disease as most important. Practically speaking, the only serious sources of tubercle bacilli now remaining are the persons who have tuberculosis, since bovine tuberculosis has become negligible as a source of infection in man. If cases can be discovered early before they have become spreaders of infection, or at least before they have been spreaders for very long, their prompt isolation and treatment should result in less infection, less tuberculosis and fewer deaths from this cause. In Detroit this concept has long been held fundamental in planning the control and ultimate eradication of tuberculosis. Extensive hospital facilities and skilled personnel, skilled in modern collapse therapy, have been made available and much has been accomplished in lessening the mortality rate. Finding the cases, however, has continued to be a process of finding far too many in the far-advanced stage when chances of recovery are not so good, and long and costly treatment is required. What is even more important many months or even years of spreading infection about them may have elapsed before these persons were discovered to have tuberculosis.

Considering how this situation might be bettered, a study of where new cases actually were first seen was enlightening in showing the volume of work done by various groups and the success of each in making diagnoses of early tuberculosis.

Of 3,680 cases with adult-type pulmonary tuberculosis on the register in Detroit in July, 1935, 1,610 had been reported by private physicians directly. Seven hundred thirty-five more were reported from general hospitals and clinics where private physicians were serving in other than special tuberculosis services, making a total of 2,325, or 63.8 per cent, which really represents the number found by private physicians. Fur-

[1] From the Department of Health, Detroit, Michigan.

[2] Presented at a session of the Administrative Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

TABLE 1

Cases of pulmonary tuberculosis on register, July, 1935

Source of report

TYPE OF TUBERCULOSIS	PRIVATE PHYSICIANS	CITY PHYSICIAN	VOLUNTARILY ENTERED BOARD OF HEALTH CLINIC	BOARD OF HEALTH CASE-FINDING	SCHOOL SURVEYS	INDUSTRIAL CLINICS	OTHER HOSPITALS OR CLINICS	OTHER	UNKNOWN	TOTAL
Adult I										
Number	218	30	78	118	26	12	119	23	33	657
Per cent	33.2	4.6	11.8	18.0	4.0	1.8	18.1	3.5	5.0	100.0
Adult II										
Number	716	83	148	168	24	23	296	51	67	1576
Per cent	45.4	5.3	9.4	10.7	1.5	1.5	18.8	3.2	4.2	100.0
Adult III										
Number	676	85	135	102	17	17	320	44	51	1447
Per cent	46.7	5.9	9.3	7.1	1.2	1.2	22.1	3.0	3.5	100.0
Total number	1610	198	361	388	67	52	735	118	151	3680
Total per cent	*43.8*	5.4	9.8	10.5	1.8	1.4	*20.0*	3.2	4.1	100.0

TABLE 2

Cases of pulmonary tuberculosis on register, July, 1935

Percentage of types of cases reported from various sources

REPORTING AGENCY	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Private physicians	218	*13.5*	716	44.5	676	42.0	1610	100.0
City physician	30	15.2	83	41.9	85	42.9	198	100.0
Voluntary entry to Board of Health clinic	78	21.6	148	41.0	135	37.4	361	100.0
Board of Health case-finding	118	*30.4*	168	43.3	102	26.3	388	100.0
School survey	26	*38.8*	24	35.8	17	25.4	67	100.0
Industrial clinics	12	23.1	23	44.2	17	32.7	52	100.0
Other hospitals or clinics	119	16.2	296	40.3	320	43.5	735	100.0
Other sources	23	19.5	51	43.2	44	37.3	118	100.0
Unknown	33	21.8	67	44.4	51	33.8	151	100.0
Total	657	*17.8*	1576	42.8	1447	39.4	3680	100.0

ther analysis, however, shows that while this large number of cases was first seen by private physicians only 13 per cent were seen first in the minimal stage.

Since such a large number of tuberculosis cases are first seen by private physicians and even though many patients wait until they are seriously ill with tuberculosis before consulting their physician, which means that they are usually in the advanced stages of the disease, we believe that it seems logical to turn to the private physician as the most important case-finder in the search for patients with tuberculosis.

The participation of the private physician in the practice of preventive medicine has been found to be successful in the control of diphtheria through immunization administered by private physicians in their own offices. Smallpox vaccination for children and food-handlers' examinations have also been done successfully by private physicians.

The successful coöperation of the county medical society in these projects made it seem feasible to approach tuberculosis case-finding on a similar basis.

In order to bring this about a campaign of education was launched designed to:

1: Enlist financial support from the community through public funds by pointing out the poor economy of large expenditures for long and costly treatment of advanced cases of tuberculosis when more money spent on case-finding would result in much lower cost to the community through the shorter hospital stay of early cases and the lessened number of cases developing through contact.

2: To arouse the public to the necessity of seeking careful examination to make certain that they individually do not have tuberculosis.

3: Education of the medical profession in the steps of the campaign; the use of the tuberculin test and the X-ray in the diagnosis of tuberculosis and the enlistment of their coöperation in providing examinations for the presumably well person.

In the first of these efforts an extensive campaign of newspaper and radio publicity served very effectively to arouse sentiment to the point where funds were made available to the extent of $200,000.00 per year for a period of five years with the understanding that a large saving to the community both in lives and dollars was likely to result in that length of time.

The newspaper, the radio, talks before special groups, and house to house visits by nurses were used to enlist the public in the campaign.

The physicians were encouraged to undertake the work by material sent them by mail, by postgraduate courses and by visits from the medical coördinator to individual physicians and to small groups of physicians.

All of this effort was undertaken jointly by the Wayne County Medical Society and the Health Department with assistance from the Detroit Tuberculosis Sanatorium Association, the seal-sale organization in Detroit.

The keen interest of the physicians is shown by the fact that over eight hundred have signed up as coöperating physicians for tuberculosis case-finding. A postgraduate course given in November, 1936, one morning a week for four weeks, had an average attendance of 225, and a similar course in April this year had an average of 135 physicians in attendance for five weeks.

In approaching the problem of case-finding with the objective of increasing the number of early cases found, it is at once apparent that persons will have to be examined for evidence of tuberculosis before they themselves have any serious suspicion that such disease might exist in their own bodies.

It is desirable that everyone have a periodic examination complete enough to rule out tuberculosis, but obviously it is not immediately possible to provide tuberculin testing and X-ray examinations for the whole population. Certain groups in the community have therefore been selected as being those where experience has taught tuberculosis is present more frequently than among others.

While several such groups might be selected, three were chosen for the beginning; namely, first, contacts to known cases; second, persons whom, for one reason or another, the doctor suspects of having tuberculosis in the course of examination for other conditions, or because of history or of symptoms; third, those persons who live in areas in which the mortality from tuberculosis is excessively high.

The method of examination used is that of tuberculin testing all children and adults in these three groups alike and making an X-ray film of the positive reactors.

Old Tuberculin is furnished to the physicians in capillary tubes suitable for the Pirquet test. The Mantoux test is used by some physicians, but most of them at present use the Pirquet test since the materials can be kept indefinitely in the office and only one test is required whereas with the intracutaneous test freshly made dilutions and often two tests are required.

The private physician makes and reads the test and reports the result to the Health Department on a special postcard form for the purpose.

If the test is positive he will then refer the patient to a coöperating roentgenologist for an X-ray examination with an interpretation based on a single flat film of the chest. This the roentgenologist reports to the original physician and also sends in a card to the Health Department indicating the result. If the physician originally doing the test has his own X-ray equipment suitable for making satisfactory chest films, he may take films of the positive reactors he has tested but it is not expected that anyone other than a recognized specialist in roentgenology will accept work referred by others.

All doubtful or positive films are reviewed by a special committee of roentgenologists in order that the grade of work done may be kept on a high plane.

After the X-ray film has been interpreted the original physician sees the patient for the purpose of observing him more closely, acquainting him with the result of the examination, and, if any disease is found, advising him as to hospitalization or other suitable care.

Payment for this service is made to the physician on a fee basis. If the patient is able to pay he pays for the test and for the X-ray examination. However, if the patient cannot pay, the physician may bill the Health Department at the rate of $1.00 for the tuberculin test including the reading and $1.00 for the final consultation in positive reactors. The roentgenologist may bill the Health Department $3.00 for the X-ray examination if the patient is unable to pay.

In order to encourage persons to go for these examinations additional nursing personnel has been placed in the field to urge contacts to known cases of tuberculosis to go to their doctors, and in the areas of high mortality house-to-house visits are made to urge all persons living in such areas to be examined.

A careful follow-up system is entrusted to the responsibility of the nurses whose duty it is to visit periodically all contacts and to encourage them to be reëxamined at regular intervals.

A full-time medical relations director, or coördinator, a physician, is a very important person in this plan. By keeping in close touch with physicians he assists in having work properly done and properly reported. Difficulties which may be encountered by the individual physician may be straightened out in conference with the medical relations director.

A carefully planned record system has been set up to keep track of all work reported and of all results obtained. This tremendous amount of

epidemiological data from the reporting of large numbers of tuberculin tests and the X-raying of large numbers of persons if properly evaluated as the work progresses will be of inestimable value.

The program has been in effect only a short time, having started in November and December of last year with the publicity. The nursing field work and intensive effort did not really get under way until February 1 this year.

Up to the present, 302 of the 850 coöperating physicians have turned in reports of 33,367 tests done. Of this number 7,472, or 22.4 per cent, are reported as positive. This percentage covers children and adults and we cannot say at this time what proportions of the various age groups are included. Individual records are kept for each physician reporting so that, when there is an unusually low or high percentage coming in, his record is more carefully studied and if necessary a conference on technique is arranged. With a few exceptions the testing is being well done.

Of the positive reactors, 5,122[3] have been X-rayed and, after careful recheck and elimination of inactive and negative cases originally reported as positive and active, the following tabulation of cases has been established:

Childhood type, active		35
Adult pulmonary:		
Minimal	72	
Moderately advanced	59	
Far advanced	32	
Total pulmonary		163
Other forms		17
Total active tuberculosis		215

These examinations have been reported by 19 roentgenologists and 14 general practitioners doing their own X-ray work.

Of the active cases, 163 were adult-type pulmonary tuberculosis of which 72 were minimal cases, or 44.2 per cent, which is a definite improvement over the previous experience of only 13 per cent minimal for the private physicians' experience and 20 per cent for the average of all the reported cases.

[3] Because of the lag between tuberculin test reports and X-ray reports, the 215 cases reported out of 5,122 X-rayed represent the number to be found from approximately 22,000 persons tested, or approximately one case in one hundred individuals.

At this point it may be well to indicate that all this work is in addition to case-finding efforts already going on in the community. As the medical participation plan shows its effectiveness and proves its complete worth it will gradually take over these other activities.

It is not planned to discontinue any service until it can be done as well or better by the new plan.

SUMMARY

A plan for medical participation in tuberculosis case-finding is presented.

First experiences with the use of this plan in Detroit are reported.

The experience while of only short duration indicates that this plan offers great promise of success in finding cases early.

TUBERCULOSIS IN CONTACTS OF CHILDREN WHO REACT TO TUBERCULIN[1]

C. W. WELLS

A tuberculosis survey in Kingston, Jamaica, concluded in February, 1934, included a total population of 7,093, of whom 78.3 per cent were tuberculin tested and 70.0 per cent received X-ray examinations of the chest. Seventy-two cases of manifest pulmonary tuberculosis, only 18 of which were previously known, were found among those examined.

The result of the intracutaneous tuberculin test is generally recognized as furnishing a fairly accurate and reliable index of tuberculous infection in any group of individuals to whom the test is applied. The correlation between the intensity of the intracutaneous tuberculin reaction and the occurrence of tuberculous infection and disease has been demonstrated (1) (2). A study of the occurrence of positive tuberculin reactions in individuals in contact with manifest pulmonary tuberculosis is of interest, since this phase of the subject may be of practical importance and deserve greater attention than it has previously received as an aid in the search for unrecognized cases of active tuberculosis (3).

The data accumulated during the tuberculosis survey in Kingston furnish valuable material for determining the association between tuberculin-positive reactors and cases of tuberculosis in the survey areas. This material has been analyzed from the standpoint of preschool and school children who were positive tuberculin reactors.

Because of peculiar conditions prevalent in Kingston, as well as in most tropical cities, the term "contact" implies more than family or household relationship. A characteristic of living arrangements among the poorer class is the custom for a number of families to congregate and live together in one yard or compound. The number of families so living may vary from two to twenty, each usually occupying a single room. Occasionally these rooms may be separate structures, but more often they are one of a series adjoining each other. In practice, all individuals

[1] This study was conducted with the support of and under the auspices of the International Health Division of The Rockefeller Foundation in coöperation with the Jamaica Government Medical Department.

living in such yards mingle as members of one large family with common kitchen and sanitary facilities, and frequently children may be found sleeping in any room but their own.

The term "children" as employed in this paper embraces both preschool and school children, separate consideration being given to each group as well as to their combination. Preschool children include all individuals under five years of age. School children embrace all individuals between five and nineteen years, inclusive, who were actually attending school. Other individuals in the five to nineteen years group are omitted from this study.

Because of the conditions described above, this paper will consider: (1) tuberculosis in household contacts of children who react to tuberculin; (2) tuberculosis in yard contacts of children who react to tuberculin; and (3) an estimate of the total number of individuals it would be necessary to examine in order to discover cases of tuberculosis if the principles described in this study were applied as a case-finding procedure.

TUBERCULOSIS IN HOUSEHOLD CONTACTS OF CHILDREN WHO REACT TO TUBERCULIN

Seventeen persons with manifest tuberculosis, representing 16 different households, were living in households containing preschool children. These households contained 24 preschool children; 23 of these were tuberculin tested, and of this number 14, or 60.9 per cent, were tuberculin-positive. All the remaining preschool children in the survey not in contact with manifest tuberculosis showed only 33.6 per cent tuberculin-positive. The 14 tuberculin-positive preschool children were in household contact with 10, or 58.8 per cent, of all cases of tuberculosis in contact with preschool children (table 1).

Thirty-four school children were in household contact with 25 cases of manifest tuberculosis. Thirty were tuberculin tested and 20, or 66.7 per cent, of these were tuberculin-positive. This compares with 65.8 per cent tuberculin-positive in all other school children not in contact with manifest cases of tuberculosis. The 20 tuberculin-positive school children were in household contact with 19, or 76.0 per cent, of all cases of manifest tuberculosis in contact with school children (table 1).

Combining preschool and school children it was found that 58 were in household contact with 32 cases of manifest pulmonary tuberculosis. Thirty-four, or 65.4 per cent, of these children were tuberculin-positive, as compared with 55.1 per cent positive reactors in all noncontact chil-

dren. The tuberculin-positive children were in household contact with 25, or 78.1 per cent, of all cases of tuberculosis in household contact with children (table 1).

Children, when considered as preschool, school, or both combined, in household contact with cases of manifest pulmonary tuberculosis, showed a higher percentage of tuberculin-positive reactions than children not so exposed. While the difference in tuberculin-positive reactions between exposed and nonexposed groups of children is not statistically significant, yet it is suggestive, particularly in the case of preschool children.

The majority of all cases of tuberculosis in household contact with children were in contact with tuberculin-positive children, the percentage

TABLE 1

Relation of tuberculin-positive children to household contact with cases of manifest pulmonary tuberculosis

CLASS OF CHILDREN	NUMBER OF CHILDREN IN HOUSEHOLD CONTACT WITH MANIFEST CASES	TUBERCULIN TEST				PER CENT TUBERCULIN-POSITIVE OF ALL OTHER CHILDREN IN SURVEY AREAS	TOTAL CASES OF TUBERCULOSIS IN ENTIRE SURVEY AREAS	NUMBER OF CASES OF TUBERCULOSIS IN HOUSEHOLD CONTACT WITH CHILDREN	NUMBER OF CASES OF TUBERCULOSIS IN HOUSEHOLD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN	CASES IN HOUSEHOLD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN, PER CENT OF TOTAL	CASES IN HOUSEHOLD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN, PER CENT OF CASES IN CONTACT WITH CHILDREN
		Number of children tested	Number positive to 0.01 mgm.	Number positive to 1.0 mgm.	Per cent tuberculin-positive						
Preschool.....	24	23	10	4	60.9	33.6	72	17	10	13.9	58.8
School.....	34	30	15	5	66.7	65.8	72	25	19	26.4	76.0
Preschool and school.....	58	53	25	9	65.4	55.1	72	32	25	34.7	78.1

ranging from 58.8 per cent in the case of preschool children to 78.1 per cent when preschool and school children were combined. On the other hand, the proportion of the total number of cases of tuberculosis in the entire survey areas in contact with tuberculin-positive children was considerably smaller. These ranged from 13.9 per cent in the case of preschool children to 34.7 per cent when preschool and school children were combined.

TUBERCULOSIS IN YARD CONTACTS TO CHILDREN WHO ARE TUBERCULIN-POSITIVE

Forty-eight persons with manifest tuberculosis were living in 46 different yards containing 101 preschool children; 93 of the preschool children were tuberculin tested, and 39, or 41.9 per cent, of these were tuberculin-

positive. This compares with 33.3 per cent tuberculin-positive in all nonexposed preschool children. Twenty-nine persons with manifest tuberculosis were in yard contact with tuberculin-positive preschool children (table 2).

Fifty-six persons with manifest tuberculosis were living in 51 different yards containing 172 school children; 146 of the school children were tuberculin tested. Of these, 112, or 76.7 per cent, were tuberculin-positive, as compared with 64.2 per cent tuberculin-positive in all non-exposed school children. Forty-nine of the 56 cases of manifest tuberculosis in yard contact with school children were in yard contact with tuberculin-positive school children (table 2).

TABLE 2

Relation of tuberculin-positive children to yard contact with cases of manifest pulmonary tuberculosis

CLASS OF CHILDREN	NUMBER OF CHILDREN IN YARD CONTACT WITH MANIFEST CASES	TUBERCULIN TEST				PER CENT TUBERCULIN-POSITIVE OF ALL OTHER CHILDREN IN SURVEY AREAS	TOTAL CASES OF TUBERCULOSIS IN ENTIRE SURVEY AREAS	NUMBER OF CASES OF TUBERCULOSIS IN YARD CONTACT WITH CHILDREN	NUMBER OF CASES OF TUBERCULOSIS IN YARD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN	CASES IN YARD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN, PER CENT OF TOTAL	CASES IN YARD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN, PER CENT OF CASES IN CONTACT WITH CHILDREN
		Number of children tested	Number positive to 0.01 mgm.	Number positive to 1.0 mgm.	Per cent tuberculin-positive						
Preschool.....	101	93	26	13	41.9	33.3	72	48	29	40.3	60.4
School.....	172	146	79	33	76.7	64.2	72	56	49	68.0	87.5
Preschool and school.....	263	239	105	46	63.2	54.1	72	65	58	80.5	89.2

Sixty-five cases of manifest pulmonary tuberculosis were found in 56 different yards containing 263 children; 239 of these children were tuberculin tested, 151, or 63.2 per cent, being tuberculin-positive, as compared with 54.1 per cent tuberculin-positive for all children in the survey areas. Fifty-eight of the 65 cases of manifest tuberculosis in yard contact with children were found in yard contact with tuberculin-positive children (table 2).

As in the case of household contact with cases of manifest pulmonary tuberculosis, children in yard contact with active tuberculosis showed a higher percentage of tuberculin-positive reactions than was found in the remaining survey children not so exposed. Again, these differences are not statistically significant but possibly are suggestive.

A very high proportion of all the cases of manifest tuberculosis in yard

contact with children were found as contacts to tuberculin-positive children, the percentages varying from 60.4 in the case of preschool children to 89.2 when preschool and school children were combined. The proportion of cases of manifest tuberculosis in contact with tuberculin-positive children, on the basis of total number of cases of active disease in the entire survey areas, was lower, these percentages varying from 40.3 in the case of preschool children to 80.5 for preschool and school children combined.

ESTIMATE OF NUMBER OF PERSONS NECESSARY TO EXAMINE IN ORDER TO FIND CASES OF ACTIVE TUBERCULOSIS, EMPLOYING THE RESULTS OF THE TUBERCULIN TEST FOLLOWED BY X-RAY EXAMINATION, AS DESCRIBED

The question arising from this study is, do the results of the analysis suggest a practical addition to methods employed in routine tuberculosis case-finding, the principle upon which the additional procedure might be based being the association between tuberculin-positive preschool and school children and manifest cases of tuberculosis. Two steps would be involved in the method: (1) the tuberculin testing of all preschool and school children, those with a positive reaction to .01 and 1.0 mgm. to receive X-ray examination to determine the possible presence of active disease in this group; (2) follow-up investigations to be made of all other contacts to tuberculin-positive preschool and school children. This investigation might be confined to a tuberculin test with X-ray examination of all individuals positive to .01 mgm. of tuberculin, such individuals receiving X-ray examination to determine the presence of active or suspected tuberculosis.

The proportion of manifest cases of tuberculosis in household and yard contact with tuberculin-positive children has been shown in tables 1 and 2. Of additional importance in considering the practicability of basing a case-finding program on the principle described in this paper would be the number of persons that should be examined in order to obtain the results shown. This phase of the subject may be considered from the standpoint both of household and yard contacts.

Estimate of Persons Requiring Examination in Relation to Household Contacts: The Kingston survey areas contained 2,093 households. In 485, or 23.2 per cent, there were preschool children. The total preschool population was 673, of whom 552 were tuberculin tested; 193 were positive to .01 mgm. and 1.0 mgm. of tuberculin. The tuberculin-positive preschool children were in household contact with 626 other individuals,

TABLE 3

Persons examined to discover given number of cases of pulmonary tuberculosis in household contact with tuberculin-positive children

	PER CENT OF TOTAL HOUSEHOLDS CONTAINING CHILDREN	TOTAL NUMBER OF CHILDREN	TUBERCULIN TEST OF CHILDREN		TUBERCULIN TEST OF HOUSEHOLD CONTACTS OF CHILDREN TUBERCULIN-POSITIVE		NUMBER OF CASES OF MANIFEST TUBERCULOSIS IN HOUSEHOLD CONTACT WITH CHILDREN	NUMBER OF CASES OF MANIFEST TUBERCULOSIS IN HOUSEHOLD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN	NUMBER OF CASES OF MANIFEST TUBERCULOSIS TUBERCULIN-POSITIVE AMONG HOUSEHOLD CONTACTS OF CHILDREN TUBERCULIN-POSITIVE	PER CENT OF ALL CASES OF TUBERCULOSIS EVENTUALLY FOUND	PER CENT OF CASES IN HOUSEHOLD CONTACT WITH CHILDREN EVENTUALLY FOUND
			Number tested	Positive to 0.01 mgm.	Total number household contacts to tuberculin-positive children	Number tested	Number positive to 0.01 mgm.				
Preschool	23.2	673	552	123	626	558	428	17	10	9	12.5	52.9
School	32.3	1238	1075	520	1691	1457	1072	25	19	15	20.8	60.0
Preschool and school	46.6	1911	1627	643	1725	1483	1191	32	25	21	29.2	65.6
				Positive to 1.0 mgm.								
				252								
			Per cent tuberculin-positive									
			55.0									

558 of whom were tuberculin tested and 428 found positive to .01 mgm. of tuberculin (table 3). Seventeen persons with manifest tuberculosis were in households containing preschool children. Only 10 of these persons were in households with tuberculin-positive preschool children. Of the 10 cases among household contacts to tuberculin-positive preschool children, 9 were positive to .01 mgm. of tuberculin; one did not receive a tuberculin test. By the proposed procedure about one-half the cases of manifest tuberculosis in household contact with preschool children would have been revealed, and, on the other hand, only about one-eighth the total cases in the entire survey areas would have been found. If all the preschool children had received a tuberculin test (121 were not tested) a larger proportion of the contact cases with preschool children might have been discovered.

There were 676 households in the entire survey areas containing 1,238 school children, of whom 1,075 were tuberculin tested, 702 being positive to .01 and 1.0 mgm. of tuberculin (table 3). There were 1,691 other individuals in contact with the tuberculin-positive school children; 1,457 of these were tuberculin tested and 1,072 were positive to .01 mgm. of tuberculin. Twenty-five persons with manifest tuberculosis were living in household contact with school children, 19 of whom were in contact with tuberculin-positive school children. Fifteen cases of manifest disease were found among tuberculin-positive contacts of the tuberculin-positive school children. The proposed case-finding procedure, if applied to school children, would have revealed 60 per cent of all cases of manifest tuberculosis in household contact with school children, but only 20.8 per cent of the cases in the total survey population. Here again it should be noted that 163 school children were not tuberculin tested. The test applied to these might have increased the number of cases of disease discovered.

Applying the principle discussed above to the combined preschool and school children slightly increased the number of cases of disease which might have been discovered. There were 975 households in the survey areas containing 1,911 preschool and school children, 1,627 of whom were tuberculin tested, 895 being positive. The tuberculin-positive children were in household contact with 1,725 other individuals, 1,483 of whom were tuberculin tested and 1,191 found positive to .01 mgm. of tuberculin (table 3, chart 1). Thirty-two persons with manifest tuberculosis were living in household contact with children; only 5 of these were previously known. In households containing tuberculin-positive children there

were 25 persons with manifest tuberculosis. Twenty-one of these were included among the tuberculin-positive contacts to tuberculin-positive children. Of the remaining four persons, two were not tested, one was positive to 1.0 mgm. of tuberculin, and one was tuberculin-negative. Two hundred eighty-four preschool and school children were not tuberculin tested. If the tuberculin test had been applied to these it might have resulted in an increase in the number of cases of manifest disease discovered.

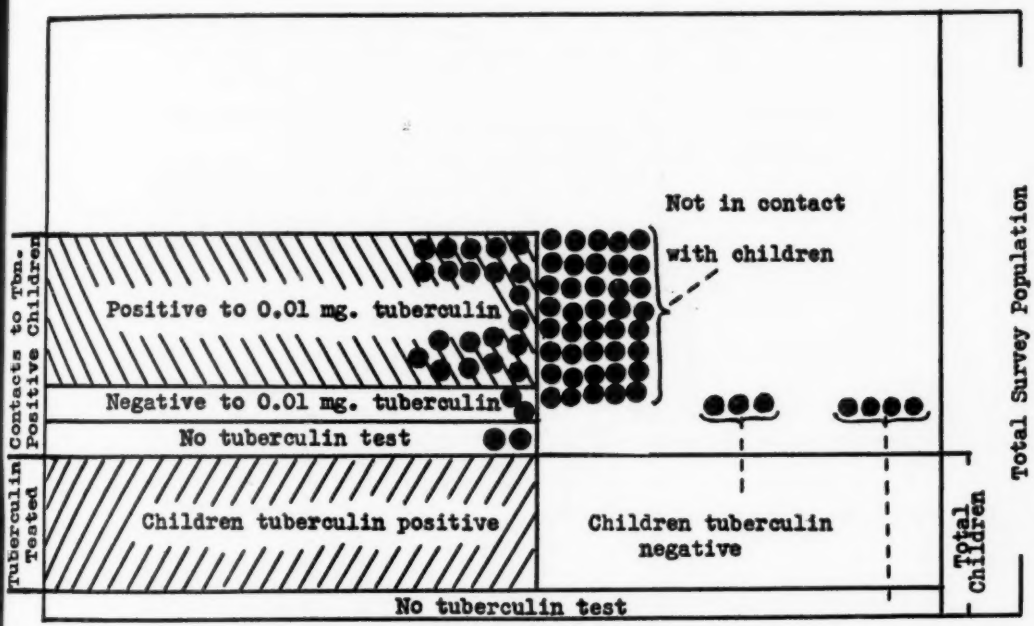

CHART 1. Relation of cases of manifest tuberculosis to household contacts of tuberculin-positive children. ● Case of manifest pulmonary tuberculosis.

Estimate of Persons Requiring Examination in Relation to Yard Contacts: As previously described, the yard as a unit for living arrangements is characteristic of the poorer population in Kingston and many other tropical cities. Individuals living in a given yard constitute to all intents and purposes one large family, involving most of the intimate relationships typical of family life. Especially is this true of children. Eating arrangements are often on a coöperative basis. Because of these conditions, it is desirable to apply the analysis described in this paper to yard contacts.

TABLE 4

Persons requiring examination to discover given number of cases of manifest pulmonary tuberculosis in yard contact to tuberculin-positive children

CLASS OF CHILDREN	NUMBER OF YARDS IN SURVEY AREAS WITH CHILDREN	TOTAL NUMBER OF CHILDREN	TUBERCULIN TEST OF CHILDREN				YARD CONTACTS TO TUBERCULIN-POSITIVE CHILDREN			NUMBER OF CASES OF MANIFEST TUBERCULOSIS IN YARD CONTACT WITH CHILDREN	NUMBER OF CASES IN YARD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN	NUMBER OF CASES IN YARD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN, FOUND AMONG TUBERCULIN-POSITIVE CONTACTS	PER CENT OF TOTAL CASES IN YARD CONTACT WITH CHILDREN	PER CENT OF CASES IN YARD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN	PER CENT OF CASES IN YARD CONTACT WITH TUBERCULIN-POSITIVE CHILDREN, FOUND AMONG TUBERCULIN-POSITIVE CONTACTS	PER CENT OF TOTAL CASES DISCOVERED BY METHOD
			Number tuberculin tested	Positive to 0.01 mgm.	Positive to 1.0 mgm.	Total positive	Total number	Number tuberculin tested	Positive to 0.01 mgm.							
Preschool.....	537	677	556	123	71	194	1630	1380	1054	48	29	25	66.7	40.3	86.2	34.7
School.....	513	1329	1148	539	193	732	3209	2659	2064	56	49	41	77.8	68.0	83.7	56.9
Preschool and school.....	580	2006	1704	662	264	926	3165	2585	2141	65	58	49	90.3	80.5	84.5	68.0

In the survey areas there were 357 yards containing 677 preschool children, 556 of whom were tuberculin tested, 194 being tuberculin-positive (table 4). There were 1,630 other individuals in yard contact with 194 tuberculin-positive preschool children; 1,380 of these were tuberculin tested, 1,054 being positive to .01 mgm. of tuberculin. Among the yard contacts of preschool children were 48 persons with manifest pulmonary tuberculosis. Twenty-nine of these persons were in contact with tuberculin-positive preschool children. Twenty-five of the 29

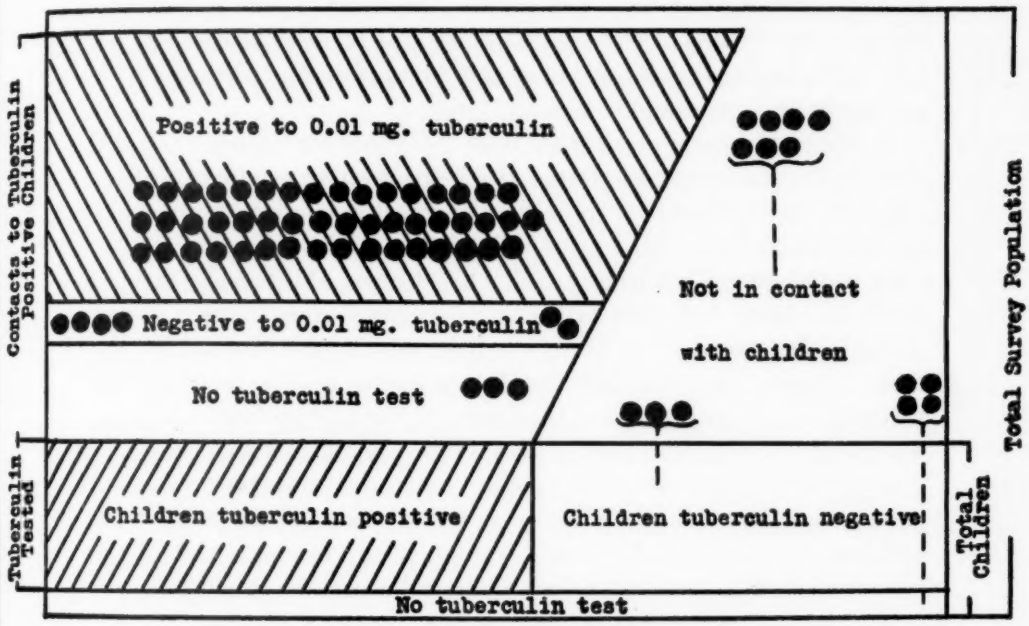

CHART 2. Relation of cases of manifest tuberculosis to yard contacts of tuberculin-positive children. ● Case of manifest pulmonary tuberculosis.

persons were positive to .01 mgm. of tuberculin; of the 4 remaining, 1 was positive to 1.0 mgm., 2 were not tested, and 1 was tuberculin-negative. This procedure applied to yard contacts of tuberculin-positive preschool children would have revealed 52.1 per cent of all cases in yards containing preschool children, 86.2 per cent of all cases in contact with tuberculin-positive preschool children, and 34.7 per cent of all cases in the total survey areas.

There were 513 yards in the total survey areas containing 1,329 school children, of whom 1,148 were tuberculin tested. Of those tested, 732,

representing 356 different yards, were positive to tuberculin. There were 3,209 other individuals in contact with the tuberculin-positive school children, 2,659 of whom were tuberculin tested, with 2,064 being positive to .01 mgm. of tuberculin. School children were in yard contact with 56 cases of manifest tuberculosis, but only 49 of these cases were in contact with tuberculin-positive school children. Of the latter number, 41 were tuberculin-positive. Three of the remaining 8 were positive to 1.0 mgm. of tuberculin, 2 were tuberculin-negative, and 3 untested. By this method 73.2 per cent of all cases of manifest tuberculosis in yard contact with preschool children, 83.7 per cent of cases in contact with tuberculin-positive school children, and 56.9 per cent of all cases in the entire survey areas would have been found.

In the total survey areas there were 580 yards containing 2,006 children; 1,704 were tuberculin tested, 926 being positive reactors to .01 and 1.0 mgm. of tuberculin. These positive reactors among children were in yard contact with 3,165 other individuals; 2,585 of these were tuberculin tested, with 2,141 being positive to .01 mgm. of tuberculin (table 2, chart 2). Sixty-five cases of active tuberculosis were in yard contact with children; 58 of these were in contact with tuberculin-positive children. Among the tuberculin-positive contacts of tuberculin-positive children there were 49 cases of tuberculosis. The remaining 9 comprised 3 who received no test, 4 positive to 1.0 mgm., and 2 tuberculin-negative. The results in the discovery of manifest cases of the disease expressed in percentages are as follows: 75.4 per cent of all cases in yard contact with children; 68.0 per cent of all cases in the total survey areas; and 84.5 per cent of all cases in yard contact with tuberculin-positive children.

DISCUSSION

A tuberculosis survey in the city of Kingston, Jamaica, resulted in the discovery of 72 cases of manifest pulmonary tuberculosis in the survey population examined. The data accumulated through this survey offered an opportunity to compare the number of cases so found with the number which might have been revealed by an examination of contacts with tuberculin-positive children. The results of other studies (1) (2) suggest the practicability of sifting contacts by the use of a single intracutaneous tuberculin test of .01 mgm. Such a procedure would materially reduce the number of contacts requiring further examination. All contacts positive to .01 mgm. of tuberculin should receive X-ray

examinations of the chest supplemented by physical examination of positive and suspicious cases.

For the purpose of this study, preschool and school children have been chosen as groups of individuals which might serve through their tuberculin reactions as indicators or reflectors of the location of tuberculous infection in the community. Both of these groups of individuals are fairly accessible, particularly school children. Home visits would probably be necessary to reach preschool children. This would entail added work but is not impracticable and might even be desirable, since it would offer an opportunity for valuable educational efforts.

The family or household is a recognized unit of society in most countries. In general, this is true in Kingston. However, certain conditions among the poorer class in this city, as well as in other tropical cities, render the family or household a less important unit from the standpoint of tuberculosis control. Large numbers of young adults of both sexes migrate to Kingston from the country parts of the island in search of employment. Such individuals are highly susceptible to tuberculous infection, not only because of the absence of previous contact with the disease, which is much less prevalent in the country areas, but also because of low standards of living characteristic of this class of individuals. Upon arriving in Kingston the newcomer seeks living quarters in the poorer section of the city where rent is low and where the characteristic arrangement for living is that previously described in this paper as "yards." Because of these conditions this paper undertakes to describe the relationship of both household and yard contacts to tuberculin-positive children.

The data shown in tables 1 and 2 have been presented graphically in chart 1. Only 32 of the 72 cases of manifest disease found in the original survey were in household contact with children. The remaining 40 cases comprised 8 individuals living alone, and 32 who were living with one or more than one adult. Obviously none of these 40 cases could have been discovered through an investigation employing children as a starting point. Only 46.6 per cent of all the households or families in the survey areas contained children. This finding may possibly be construed as a point against the practicability of the principle discussed in this paper as a basis for case-finding procedure. On the other hand, in other countries a larger proportion of the households may contain children. In the survey population employed for this study, 23.2 per cent of the house-

holds contained preschool children. On the other hand, in the Eastern Health District of Baltimore for 1933, 25.1 per cent of white households and 32.7 per cent of colored households contained preschool children.[3]

A certain number of persons with manifest tuberculosis may be in household contact with children who give a negative reaction to tuberculin. In the Kingston survey areas there were 3 such persons. Also there were 4 persons with manifest tuberculosis in household contact with children who were not tuberculin tested. If the search for cases among the contacts of tuberculin-positive children were confined to those who were positive to .01 mgm. of tuberculin, 2 persons with manifest disease would have been missed because of their failure to give a positive reaction to the dose of tuberculin employed. One of these persons was positive to 1.0 mgm. and the other was negative. Two persons with manifest disease who were in contact with children were not reached by the tuberculin test. They were included in a group of individuals who received chest X-ray examination but refused to submit to the tuberculin test.

The search for cases of manifest pulmonary tuberculosis among the household contacts of tuberculin-positive children, as determined from an analysis of the survey data, would have resulted in the finding of 21 cases out of a maximum total of 25 cases, a percentage of 84.0. This number would have been only 29.2 per cent of all the cases found in the original survey, and 65.6 per cent of cases in household contact with children.

A further point of importance in evaluating the merits of the procedure under discussion is a determination of the number of examinations required to discover the 21 cases. This may be derived from table 3. The examinations comprised tuberculin tests and X-ray examinations, the latter being confined to children positive to 0.01 and 1.0 mgm. of tuberculin and contacts positive to .01 mgm. of tuberculin. A total of 3,110 tuberculin tests were given, averaging 148 tests per new case of manifest disease discovered; 2,086 individuals, including children as well as contacts, were tuberculin-positive, and if these had been given X-ray examinations, it would have meant an average of 99.3 individuals X-rayed for every new case discovered.

A similar analysis of yard contacts reveals a more suggestive picture. On this basis only 7 of the 72 persons with tuberculosis found in the original survey were not in contact with children. Three additional persons

[3] Personal communication from Dr. Lowell J. Reed, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland.

were in contact with tuberculin-negative children, and 4 were in contact with children who were not tuberculin tested. Of the 58 persons with manifest tuberculosis who were in contact with tuberculin-positive children, 6 were negative to .01 mgm. of tuberculin; 4 of these were positive to 1.0 mgm. and 2 were negative to this dose. Three did not receive a tuberculin test. Forty-nine of the 58 persons in contact with tuberculin-positive children were positive reactors to .01 mgm. of tuberculin and represent the number of cases of manifest disease which would have been uncovered through a study of yard contacts. This represents 84.5 per cent of the 58 cases in yard contact with tuberculin-positive children and 68 per cent of the 72 cases found in the entire survey population.

The finding of 49 cases of manifest tuberculosis on the basis of yard contact would have required the tuberculin testing of 87.5 individuals and X-ray examination of 62.6 individuals for each case of tuberculosis uncovered.

The importance of the tuberculin test as an indication of tuberculous infection and disease is well recognized. The subject discussed in this paper suggests a possible wider application of the test in the search for new cases of disease. Such use of the test has been applied to the data derived from a tuberculosis survey in Kingston, Jamaica. The analysis suggests that such application might be practicable and produce profitable results.

SUMMARY

An analysis of the data derived from the tuberculosis survey in Kingston, Jamaica, shows that the X-ray examination of persons living in household contact with children who react to tuberculin would have revealed 29.2 per cent of the manifest cases found during a house to house survey of the community and 65.6 per cent of the cases among persons living in household contact with children. The analysis also shows that X-ray examination of persons living in yard contact with children who react to tuberculin would have revealed 68 per cent of the manifest cases found during a house to house survey and 75.4 per cent of the cases among persons living in yard contact with children.

REFERENCES

(1) Opie and McPhedran: Amer. Rev. Tuberc., 1926, *14*, 347.
(2) Wells and Smith: Ibid., 1936, *34*, 425.
(3) Brown: Public Health Nursing, 1936, *28*.

SUPPLEMENT

Discussions with a number of individuals interested in the subject of this paper, after its preparation, have suggested the desirability of further analysis of the data to show the relation of tuberculin-positive reactors in the lowest age groups to cases of manifest tuberculosis. Table 5 indicates this relation, both for household and yard contacts.

Under conditions obtaining in the Kingston survey population, 1 case of manifest tuberculosis was found in household contact for every 6 tuberculin-positive infants under 1 year of age. For children 1 to 1.9 years of age, the ratio was 1 to 16.5; whereas for children 0 to 4.9 years of age, the ratio was 1 to 21.4.

TABLE 5

Relation of tuberculin-positive children to cases of manifest tuberculosis

HOUSEHOLD CONTACTS					YARD CONTACTS				
Age	Number of children	Number of children tuberculin-positive	Number of cases of manifest tuberculosis in contact with tuberculin-positive children	Ratio of cases of manifest tuberculosis to tuberculin-positive children	Age	Number of children	Number of children tuberculin-positive	Number of cases of manifest tuberculosis in contact with tuberculin-positive children	Ratio of cases of manifest tuberculosis to tuberculin-positive children
0–0.9	134	18	3	1:6	0–0.9	134	18	6	1:3
1–1.9	137	33	2	1:16.5	1–1.9	137	35	9	1:3.9
0–4.9	673	193	9	1:21.4	0–4.9	677	194	25	1:7.8

Analysis of yard contacts reveals a more striking relationship. In individuals 0 to 0.9 years of age, the ratio was 1 case of manifest tuberculosis to 3 tuberculin positive infants, and for children 1 to 1.9 years of age, the ratio was 1 to 3.9; while for the entire preschool age group, 0 to 4.9 years of age, the ratio was 1 to 7.8.

This supplementary analysis does not include reference to the proportion of all of the cases of manifest tuberculosis in the combined survey areas which might have been discovered by this procedure. It is obvious that the net results in terms of the total cases in different communities would vary, dependent in part upon the proportion of households containing preschool children.

The foregoing analysis indicates the importance of a tuberculin-positive reaction in infants and suggests a wider application of the tuberculin test to all infants as a routine procedure in baby clinics.

FACTORS INFLUENCING THE COURSE OF TUBERCULOUS INFECTION IN YOUNG CHILDREN [1,2,3]

MIRIAM BRAILEY

The Harriet Lane Tuberculosis Clinic in the out-patient department of the Johns Hopkins Hospital has been operating for the care of childhood tuberculosis since its organization by Dr. E. A. Park in 1928. Admissions to the special clinic are limited to infants who, before two years of age, are shown to be either infected with tuberculosis as demonstrated by a positive tuberculin test, or who are in imminent risk of infection because of familial contact with sputum-positive patients. After the patient has been registered in the clinic, supervision and study are continued as long as possible, but as the clinic was established only in 1928, not many of these patients have been under observation more than eight years.

In 1934 the records of all patients admitted during the five-year period between 1928 and 1933 were compiled, and from the total registration all those were selected who were tuberculin-positive before two years of age, had an X-ray of the chest at the time of the test, and had been known to the clinic at least one year unless dying sooner. The mortality from all causes of this group, who numbered 170, was the subject of a paper published by this author in 1936.[4]

The present note adds more than two years' experience to the records of the original 170, and presents data on 53 new patients admitted between 1933 and 1936. These fulfil the same conditions and raise the number under observation to 223, of whom 91 are white and 132 are colored.

In measuring the mortality which these infants have suffered over a

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[2] This study was aided by grants from the Commonwealth Fund, the Milbank Memorial Fund and the Maryland Tuberculosis Association.

[3] Presented in part at a session of the Clinical Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

[4] *Bulletin of the Johns Hopkins Hospital*, July, 1936, *59*, 1.

period of years, it is apparent that the death-rate for the *first* year of clinic observation can be expressed simply as a percentage of the whole number of patients registered. But for periods longer than one year, the number under observation is diminished as time is extended, and in consequence a somewhat more elaborate procedure is necessary for calculating rates of mortality.

The method is explained and illustrated in the original paper. Basic data used in the calculation of mortality for the present paper are shown in table 1.

Table 2 shows in summary form, for white and colored, the mortality from tuberculosis during the first year, the first five years, and the whole eight-year period of observation following the discovery of infection. In both races the first year subsequent to the discovery of infection was most dangerous. In the white race 80 per cent of all mortality from tuberculosis occurred during the first year of observation and all had occurred by the end of five years. In the colored children of our series 51 per cent of the total eight-year mortality fell within the first year of known infection. Deaths continued, however, after the first year, two-thirds of the total mortality having occurred by the end of the first five years, the final third taking place in the fifth to eighth years of observation. It should be remembered that all the patients of this study entered observation during infancy, the average age being 13 months for children of both races.

It is to be noted from table 2 that at every time-period shown the colored suffered a mortality at least twice that of the white. For the first year of clinical observation, mortality was about 9 per cent for the white and 18 per cent for the colored; at the end of five years it had risen to 10 per cent for the white and to 22 per cent for the colored; for the whole eight-year period it remained at 10 per cent for the white, but had risen to 34 per cent for the colored.

From this table it is clear that the prognosis of tuberculosis in early childhood is intimately related to race, the colored suffering a mortality in our experience from two to three times that of the white. For both races the greatest risk for children infected in infancy and followed eight years thereafter was found to lie during the first year of known infection.

When the 223 patients are classified according to X-ray findings on admission, it is found that 94 had definite lesions in the pulmonary parenchyma usually associated with enlarged tracheobronchial lymph nodes. Somewhat over one-third of these, 35, were actually ill when first

TABLE 1

Basic data for calculation of mortality in 91 white and 132 colored tuberculin-positive infants followed for periods varying from one to eight years

TIME PERIODS IN YEARS AFTER INITIAL X-RAY EXAMINATION	(1) NUMBER UNDER OBSERVATION AT BEGINNING OF PERIOD	(2) NUMBER WITHDRAWN ALIVE FROM OBSERVATION DURING PERIOD	(3) NUMBER DYING DURING PERIOD: Tuberculosis	(4) NUMBER DYING DURING PERIOD: Other causes*
		White		
1	91	0	8	1
2	82	7	1	0
3	74	4	0	0
4	70	14	0	0
5	56	19	0	1
6	36	5	0	0
7	31	7	0	0
8	24	15	0	0
		Colored		
1	132	0	23	2
2	107	8	3	1
3	95	19	2	1
4	73	16	0	0
5	57	17	0	1
6	39	13	0	1
7	25	11	1	0
8	13	7	1	0

* In calculating the mortality from tuberculosis, the eight children dying of other causes were treated as if withdrawing alive from observation, and were added to those in that column.

TABLE 2

Mortality from tuberculosis during various time-periods after discovery of infection in 91 white and 132 colored children found to be tuberculin-positive before 2 years of age

INTERVAL FROM DISCOVERY OF INFECTION	NUMBER OF DEATHS DURING INTERVAL: White	NUMBER OF DEATHS DURING INTERVAL: Colored	MORTALITY PER CENT DURING INTERVAL* : White	MORTALITY PER CENT DURING INTERVAL* : Colored
First year	8	23	8.8	17.6
First 5 years	9	28	10.0	21.9
First 8 years	9	30	10.0	33.7

* The mortality rates shown in table 2 represent the probabilities of dying within stated periods of time and are derived by actuarial method from the data shown in table 1. Tables 3 and 4 are also summaries, similarly derived from basic data which are not shown in this paper.

seen and presented fairly conclusive evidence of pulmonary tuberculosis apart from roentgenological findings. The remaining 59 with parenchymal lesions could not have been diagnosed without the aid of tuberculin and X-rays. The majority of them came to the pediatric dispensary only on request, because of contact with tuberculosis in some relative; the rest, seen for nonspecific complaints, were discovered to be infected when a routine tuberculin test was applied.

There were 129 children with no X-ray evidence of parenchymal lesion when found to be infected. These consisted of 44 who presented bulging mediastinal shadows and were regarded as cases of uncomplicated tuberculosis of the tracheobronchial lymph nodes, and 85 who, although tuberculin-positive, gave no definite X-ray evidence of chest lesion when first seen. The mortality from tuberculosis in children of our series admitted without parenchymal lesion proved to be about the same whether the initial plate showed a bulging node or no definite abnormality, and accordingly all 129 patients have been considered together.

The mortality of patients, according to the presence or absence of parenchymal involvement in the initial X-ray film, is shown in table 3. During the first year of clinic observation, 26 deaths from tuberculosis occurred among the 94 patients admitted with parenchymal lesion, a mortality of 28 per cent and, surprisingly enough, very nearly the same for the two races. This had risen to 30 per cent by the end of five years, and to 39 per cent by the end of eight years. With respect to mortality after the first year of observation, the numbers observed are too small to afford a significant statistical basis for comparing white and colored. It is, however, to be noted that in the small group of colored children observed more than five years—children whose ages would be between six and ten years of age—there were two deaths from tuberculosis, whereas no deaths occurred among the white children after the first year of known infection. Considered by itself this difference in mortality is not statistically significant. It may, however, be associated with other facts indicating characteristic differences between white and colored children in their reaction to tuberculosis at this age. Thus, X-ray examinations made in the Harriet Lane Tuberculosis Clinic show that, in general, colored children who have survived parenchymal lesion as long as five years show more evidence of continued pathological activity than do white children during the same period. Also, in Maryland, records of mortality in recent years show that the ratio of disparity between white and colored in the tuberculosis death-rate is greatest between five and fifteen years of age.

In table 3 is also shown the mortality from tuberculosis of the 129 infants admitted without X-ray evidence of parenchymal involvement. When no separation is made for race, their first-year mortality was about 4 per cent, rising to 7 per cent at the end of five years, no increase occurring during the final three years of observation. Their final eight-year mortality rate of 7 per cent was less than one-fifth of that observed for children admitted with parenchymal lesions.

In this group, admitted without parenchymal lesions, there was a marked difference in the mortality of the two races. The first-year mortality for the white children admitted without definite parenchymal involvement was zero; for the colored it was 7 per cent. In five years,

TABLE 3

Mortality from tuberculosis in 223 tuberculin-positive infants during various time-periods following the discovery of infection: according to lesion shown at initial X-ray examination

RACE	NUMBER OF CASES	DEATHS FROM TUBERCULOSIS					
		Within 1 year		Within 5 years		Within 8 years	
		Number	Per cent	Number	Per cent	Number	Per cent
Parenchymal lesion in first X-ray							
White	32	8	25.0	8	25.0	8	25.0
Colored	62	18	29.0	20	32.4	22	47.3
Total	94	26	27.7	28	29.9	30	38.7
No parenchymal lesion in first X-ray							
White	59	0	—	1	1.8	1	1.8
Colored	70	5	7.2	8	12.3	8	12.3
Total	129	5	3.9	9	7.4	9	7.4

for the white mortality was still less than 2 per cent, for the colored 12 per cent. After five years of observation no additional deaths from tuberculosis occurred among the children of either race.

The total number of deaths from tuberculosis among the 223 patients in the eight years of clinical observation was 39. In children admitted with parenchymal lesions, a total of 30 deaths occurred. Twenty-six of these (87 per cent) were due directly to extrapulmonary disease, notably tuberculous meningitis (18 instances) and generalized tuberculosis (8 instances). In the remaining four patients, the disease was thought to be mainly pulmonary. Only one of these came to autopsy. A second case died at 7 years of age of pulmonary haemorrhage from a large cavity.

In children admitted without definite parenchymal involvement, there were 9 deaths from tuberculosis over an eight-year period. All nine died of extrapulmonary tuberculosis; one from generalized tuberculosis, eight from tuberculous meningitis. In three of the nine, parenchymal lesions developed under observation. In the remaining six no such involvement was observed during life, but of these, three coming to autopsy showed definite lesions in the lung proper.

Colored patients of this series showed parenchymal lesions on admission in 47 per cent of the cases, the white in 35 per cent. Within the first year of observation white patients admitted without lung involvement had developed it in less than 2 per cent, the colored in 23 per cent. In five years' time the proportion of white patients developing parenchymal lesion after admission had risen to 4 per cent, that of the colored to 31 per cent. No new instances were observed in either race in the remaining 3 years of observation.

TABLE 4

Mortality from tuberculosis during various time-periods after the discovery of infection in 223 infants, according to age in months when tuberculin was found to be positive

AGE IN MONTHS AT FIRST KNOWN POSITIVE TUBERCULIN	NUMBER OF CASES	DEATHS FROM TUBERCULOSIS					
		Within 1 year		Within 5 years		Within 8 years	
		Number	Per cent	Number	Per cent	Number	Per cent
0–6	27	6	23.5	8	32.9	8	32.9
6–24	196	25	12.8	29	15.0	31	20.3
Total.....	223	31	14.0	37	17.0	39	21.9

It is of interest to find that children known to be infected before six months of age had a tuberculosis death-rate within the first year of clinical observation nearly twice as great as children found to be infected between six months and two years of age. In this series, children found to be infected between six months and one year suffered a mortality not very different from those infected during the second year of life. It is possible, however, that larger numbers would disclose a difference. In table 4 mortality from tuberculosis at various time-periods is shown for infants whose infection was discovered before six months of age and for those found tuberculin-positive between six months and two years of age. Within the first year of clinical observation, 24 per cent of those *known* to be infected before six months of age had died, and additional

deaths brought this mortality up to 33 per cent by the end of five years, no further deaths occurring between the fifth and eighth years of observation. For children whose infection was discovered after the sixth month but before two years of age, the first-year mortality was 13 per cent, rising to 15 per cent by the end of five years, and to 21 per cent by the end of the whole eight-year period.

It is generally believed that prolonged household exposure tends to increase the severity of infection as expressed by mortality from tuberculosis among those infected. For children of this series detailed records have been kept of all known exposure to sputum-positive or fatal cases within the household. In 77 per cent of the white and 64 per cent of the colored children of this series more or less prolonged association with an infective case was demonstrated and it is possible that such association may have existed in a somewhat greater proportion of cases, since complete examinations of all contacts could not be carried out in every instance.

Analysis of these records shows that, counting from the date of known infection, mortality has been no higher among infants with a history of intimate exposure than among those whose exposure history was negative. However, this simple statement by no means disposes of the question, and justifies no conclusion except perhaps that the relationship between prolonged exposure and severity of infection is not so prominent and obvious in this series as might have been expected.

SUMMARY

1. A series of 223 children, of whom 91 were white and 132 were colored, found to be tuberculin-positive before two years of age, have been followed in the Harriet Lane Tuberculosis Clinic for periods ranging from one to eight years. They afford material for a study of the factors influencing prognosis in the tuberculosis of infancy.

2. They can be divided into 94 who showed parenchymal involvement at the time infection was discovered and 129 who showed no definite parenchymal lesion at initial X-ray examination. Thirty-five, somewhat more than one-third of those with pulmonary lesions, were ill and presented signs of disease such that a diagnosis could usually have been made by ordinary clinical means. The remainder gave no indication of their infection, and diagnosis could not have been made without the use of tuberculin and X-rays.

3. Over an eight-year period the mortality from tuberculosis was

three times greater in colored children (34 per cent) than in white children (10 per cent).

4. The first year of known infection was the most dangerous. More than three-fourths of the mortality in white children, and one-half of the mortality in the colored fell within the first year of observation subsequent to the discovery of infection.

5. Children admitted with parenchymal lesions suffered a mortality of 28 per cent during the first year of clinic observations, the rates being similar for white and colored. No deaths occurred among white children of this group after the first year of observation, but additional deaths raised the eight-year mortality for the colored to 47 per cent.

6. As to children presenting no X-ray evidence of parenchymal involvement on admission, no deaths occurred among white children during the first year of observation, but mortality for the colored was 7 per cent. At the end of eight years of observation the mortality for the white children was less than 2 per cent, for the colored 12 per cent.

7. Although the immediate cause of death was almost always tuberculous meningitis or generalized tuberculosis, this hazard was much greater for children admitted with parenchymal lesions than for those whose initial X-ray showed no such involvement. The colored, both on admission and throughout the period of observation, displayed parenchymal lesions much more frequently than the white, and this appears to account for their higher mortality.

8. In both white and colored children, mortality from tuberculosis has been nearly twice as high for infants known to be infected before six months of age than for those whose infection was discovered between the ages of six months and two years.

9. In 77 per cent of the white and 64 per cent of the colored children of this study there was intrafamilial contact with a proved sputum-positive case. The children with known exposure did not show a mortality significantly higher than the group for whom no such contact could be found. Study of a larger series will be necessary to determine the bearing which continued exposure may have upon prognosis.

The assistance of Dr. W. H. Frost, Professor of Epidemiology, Johns Hopkins University School of Hygiene and Public Health, who directed the analysis of data from clinical records, is gratefully acknowledged.

THE LATENT OR SMOULDERING STAGES IN TUBERCULOSIS[1,2,3]

J. ARTHUR MYERS

Since Koch discovered the tubercle bacillus in the tissues of persons who were apparently healthy there has been a great deal of interest manifested in the period intervening between the entrance of pathogenic microörganisms into the body and the appearance of illness caused by them. Recently, K. F. Meyer (1) discussed the subject of latent infections and called attention to the terms that have been employed to describe these conditions, such as "symptomless," "*inapparente*," "invisible," "silent or resting," and "quiescent" infections, also "latent microbismus" and "immunosatoric latency."

It has been observed that when blood from an animal infected with typhus is introduced into the bodies of guinea pigs, the characteristic temperature elevation sometimes fails to appear. However, the presence of the virus in such animals has been definitely proved. When immune serum and virus are introduced simultaneously into the bodies of animals, an infection occurs but there is no febrile reaction. Indeed, none of the typical symptoms, such as loss of weight and monocytosis, develops. The only obtainable evidence is a temporary increase of the neutrophiles and lymphocytes which occurs at the time when fever appears in the animals which had only the virus introduced. Nicolle opposes the use of the term "latent" but recommends that such conditions be designated as "*inapparente*" infections.

The fact is well established that the spores of the tetanus bacillus may remain in the bodies of animals over long periods of time without causing any illness. However, certain chemicals or bacterial products introduced into the animal's body result in reactivation and illness from tetanus appears. This phenomenon has also been observed in the human body

[1] From the Departments of Preventive Medicine and Internal Medicine, University of Minnesota, and the Lymanhurst Health Center, Minneapolis, Minnesota.

[2] Prepared with the aid of a grant from the Medical Research Fund, University of Minnesota.

[3] Presented before the Joint Session of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Sanatorium Association, Peoria, Illinois, September 25, 1936.

when anaerobes have been introduced through wounds with no immediate symptoms of the disease they are capable of producing. However, months or even years later an operation performed in an aseptic manner may be followed by a severe tetanus or gas gangrene. In the meantime there probably has been no multiplication of the microörganisms in the scar nor was there any evidence of an immunity which had prevented the spores from developing. It has been shown that in healthy tissues the normal oxygen tension is sufficient to prevent the germination of such spores. However, if that tension is reduced, as may occur when an inflammatory process results in hindrance of oxygen diffusion, or when the leucocytes increase the demand on oxygen, the spores may germinate. Thus, it appears to be not a matter of resistance of the host but rather a matter of creating a favorable environment for the germination of the spores. This state of inactivity of anaerobic spores in living tissues is designated as "silent or resting microbismus."

Such diseases as tuberculosis, psittacosis, and leprosy have varying periods between their entrance into the body and the development of serious clinical disease. Doerr classifies them as acyclical or chronic processes, the same as tetanus, gas gangrene, and others, but does not consider the term "silent microbismus" as applicable but prefers the term "quiescent" infections, inasmuch as no one has demonstrated an absolute or complete inhibition of the growth activities of the microorganisms. Since the diseases with a tendency toward latency rarely reveal regular incubation times, they are much more difficult to combat and to study epidemiologically than such diseases as typhoid fever and diphtheria, which have a quite definitely fixed time between the entrance of the microörganisms and the development of symptoms of the disease.

Latency may occur "as a precursor of the malady" for a matter of a few days or much longer. Again, it may occur "as a sequel of an infectious disease" when for months, years, or even a lifetime after recovery from all symptoms the microörganisms may be eliminated from the body in the secreta and excreta. In some diseases, latency occurs "as an intermediary stage;" that is, there are periods of latency alternating with exacerbations or relapses.

It is not always clear as to why a latent infection is converted into clinical disease. Some are of the opinion that the microörganisms multiply irregularly and this accounts for the microbial showers. A growth cycle of the microörganisms is a possibility. Recent studies have shown that the cellular activity of the host is important. For

example, splenectomy is sufficient to convert latent plasmodial infections of animals into severe disease. Latent conditions may be converted into serious disease by introducing material from infected organs to new hosts. On the other hand, manifest disease may be changed to a latent condition by transferring material from the involved organs to other animal species.

The organ or part of the body in which the microörganisms find lodgment may have considerable to do with the period of latency. For example, when tubercle bacilli are filtered out in a lymph node they set up foci of disease but often they do not produce evidence of manifest disease. Pneumococci are usually apparently harmless on the mucous membranes of the upper respiratory tract; that is, they produce no symptoms, but when transferred to the lung manifest pneumonia may result. Latency may also be due to encapsulation of the diseased area, fibrosis, and calcification of the involved tissues. If the number of microörganisms is small, such defense on the part of the body may suffice to prevent the disease from ever becoming sufficiently extensive to produce clinical manifestations.

Fluctuation in virulence of microörganisms is believed by some to be responsible for periods of latency. Again, the transformation of a microörganism from a pathogenic to a nonpathogenic variety is believed by others to be responsible. Still others are of the opinion that it is a matter of life cycles of microörganisms, such as tubercle bacilli and *Spirocheta pallida*, in which there may exist invisible forms of the disease agents. The metabolism of proteins, carbohydrates, and fats may have something to do with periods of latency and exacerbations. Menkin (2) has shown that in an inflammatory exudate when the reaction is approximately neutral, the number of polymorphonuclear leucocytes and mononuclears is approximately equal, but when the exudate is alkaline the percentage of polymorphonuclears exceeds that of the mononuclears. When the reaction is acid, the polymorphonuclear leucocytes degenerate in large numbers and the mononuclears are present in abundance. It is a well-known fact that monocytes play an important rôle in controlling tubercle bacilli in the animal and human body. Moreover, in the infections against which mononuclear leucocytes play a prominent part, latency frequently occurs. Therefore, it is possible that the hydrogen-ion concentration at the site of invasion may be at least one of the determining factors which initiate latency. The environment of the disease agent changes greatly during the course of an infection. It is possible

in diphtheria, for example, that the antitoxin content in the blood constantly neutralizing the toxin produced by the microörganism accounts for latency in the diphtheria carrier. Thus, the host produces a substance which conditions the latency. Immunity reactions which result from an actual attack of some diseases suffice to prevent reinfections from passing beyond the clinically latent state. For this, Doerr uses the term "immunosatoric latency."

Tuberculous disease in the human body really begins when a neutrophile phagocytoses the first tubercle bacillus; the next steps are focalization, tubercle formation, dissemination to regional lymph nodes, and the appearance of allergy. From the foci of bacilli laid down during the development of the first infection, bacilli may reach adjacent tissues at any subsequent time by direct extension, may be discharged into bronchial ramifications, into the lymph or blood-stream, into serous cavities, etc. Wherever bacilli find lodgment in allergic tissues, they are capable of setting up reinfection type of disease. If it happens to be in the meninges, or if numerous vital organs are involved because of a wide dissemination through the blood-stream, they usually lead to a rapid and fatal termination. If they lodge in other parts of the body which are not so vital because of large reserve capacity, such as the lungs or kidneys, chronic disease results which may continue in its progress until there is so much destruction of the organs that they cannot perform the required work to keep the body alive. Throughout the entire course of the disease, from the time the first neutrophile is involved until the body of the host dies of chronic tuberculosis, the bacilli may be temporarily controlled; indeed, in the first-infection type of tuberculosis they may completely die out. It is only when one is certain that all bacilli are dead, however, that one can speak of tuberculosis as being healed in the true sense of the word.

Throughout much of the time required from the beginning of tuberculosis to a fatal termination, no external manifestations are present. When the first-infection type of disease begins with ingestion of bacilli by the neutrophiles through focalization and the laying down of the framework of tubercle, there are no symptoms. In some individuals when allergy reaches a high degree, there is a temperature elevation and other mild symptoms may be experienced; the red-cell sedimentation rate is increased, but these symptoms and findings are fleeting. With rare exceptions they are not recognized as a part of the development of tuberculosis. Even after chronic reinfection forms of the disease develop and symptoms have appeared, there are frequently periods of remissions

and exacerbations. During the periods of remission, the body of the host often appears perfectly well. These periods may be of short or long duration. It is this characteristic of the disease that has led to such terms as "latent," "quiescent," "apparently arrested," "arrested," and "apparently cured." Although these terms have been used very extensively in the classification of patients, in reality they mean little or nothing with regard to the finer details of the progress of tuberculosis. We arrive at them through crude and gross manifestations, such as the presence or absence of symptoms, physical signs, laboratory findings, and shadows on X-ray film.

The latent period in tuberculosis has been largely responsible for retarding progress in the control of this disease among animals and man; for example, in 1901 Pearson and Ravenel (3) said: "There is scarcely a subject related to agriculture or public health that has occasioned as much or as bitter discussion or has led to the expression of so many divergent views as this one of tuberculosis of cattle." Pearson was a veterinarian and Ravenel a bacteriologist. At the time they made this statement the tuberculin test had been in use to detect the disease among cattle in this country for only ten years, and Doctor Pearson was one of the first to use it. The main reason for so much bitter discussion and the expression of many divergent views was that during the ten years a small group of veterinarians had recognized the latent or smouldering stage. The facts obtained by them completely contradicted most of the theories and opinions held by the majority of workers. As the new movement gained momentum, the opposition was pushed aside and there emerged a group of workers who have practically eradicated tuberculosis from cattle.

It is of interest to know around what subjects the opposition to the new progressive movement centered its attack. The conservative group clung to the belief that tuberculosis among cattle could be detected by physical examination. The progressive group brought forth proof to show that this usually was not true except after the disease had reached an advanced stage and even then it could not always be detected by this method.

The conservative group believed that symptoms were a satisfactory criterion of the presence of tuberculosis in the animal body, whereupon the progressive group brought forth abundant proof that animals with tuberculosis usually pass through a long latent or presymptomatic stage; that symptoms are a late manifestation and may not be present until the disease is far advanced.

Laboratory examinations of excreta were held by the conservative

group to be adequate in diagnosis, but the progressive group showed that the presence of tubercle bacilli in excreta usually is a manifestation of advanced tuberculosis and by the time the disease is detected in this manner, the bacilli are being passed on to other animals and human beings.

The conservative group condemned the use of tuberculin as a diagnostic agent, but the progressive group cited their postmortem evidence showing that animals with no physical signs or symptoms of tuberculosis, often appearing to be the healthiest in the herd, but reacting positively to the tuberculin test, could have tuberculous lesions easily detected by gross examination.

The minority group early called attention to the fact that the degree of reaction to tuberculin apparently had no constant relation to the extent of disease and that animals with latent tuberculosis would react as intensely or more so than those with clinical disease; they also taught that the tuberculin test is not perfect, for the occasional animal with tuberculosis fails to react. After this fact had been frankly and honestly presented and had been considered of minor significance, tuberculin was again severely attacked by the conservative group. In fact, this group devoted much time to discussing the rare insignificant exceptions rather than the usual result of the test.

Many members of the conservative group were not convinced of the contagiousness of tuberculosis among cattle, although the progressive group had the best of evidence obtainable through the work of Villemin, Cohnheim, Koch, and many others, as well as their own actual observations to prove their point. The long period between exposure and illness or the latent period was probably responsible in part for the failure of the conservative group to recognize the contagiousness of the disease. However, throughout the literature the progressive veterinarians have constantly referred to tuberculosis as contagious.

In 1892, Bang (4) of Denmark developed a method of control which bears his name. It consisted of destroying all ill animals and testing with tuberculin all healthy animals. The owners were required to isolate all positive reactors (those with latent tuberculosis) from the negative reactors. This meant the maintenance of two separate herds. At birth, the calves of the contaminated animals were immediately removed from the herd and fed on milk from the uncontaminated herd or milk that had been so heated as to destroy tubercle bacilli. These calves remained free from tuberculosis, provided they were not subsequently

exposed to tuberculous animals. This method was early adopted in such states as Pennsylvania and Wisconsin, but it was observed almost constantly that among the healthy-appearing, positive-reacting herd with latent disease, animals were reaching the symptomatic stage and were eliminating from their bodies tubercle bacilli. This, together with the inconvenience of maintaining two separate herds on the same farm, led to the present method consisting of immediate slaughter of all positive tuberculin reactors, with the result that forty-two of our states are now accredited and in all probability during 1937 all of the states will be accredited with the exception of two.

During the campaign against tuberculosis in cattle, numerous persons have come forth with methods of vaccination. Each has been given fair and sufficient trial in this country but one after the other, including the most recent, BCG, has failed of acceptance. Members of the progressive group have repeatedly called attention to the fact that individuals who have suffered an attack of tuberculosis and have recovered, at least temporarily, are not protected against subsequent attacks or recurrences and that such facts do not argue in favor of a protective vaccination. In other words, the veterinarian has not been able to countenance a procedure which leaves in the field animals with latent lesions which at any moment may spread tubercle bacilli to other cattle or human beings.

To-day in dealing with tuberculosis among human beings, we find ourselves in about the same position as the veterinarians were thirty-five years ago, when Pearson and Ravenel made their statements with regard to bitter discussions and divergent views. Krause (5), about ten years ago, made statements and raised questions, based on experience and judgment, which were destined to revolutionize completely our thinking and activities with regard to tuberculosis and its control in the human family. Let us examine some of his statements of 1926.

"I am inclined to believe that children with tuberculous infection are becoming fewer. No doubt much of my belief rests upon the shaky premise that such ought to be the case. . . . Until lately I was always inclined to look with some suspicion on reports of the incidence of childhood infection (as determined by skin tests), which made this unusually low according to our standard ideas formed largely between 1910 and 1915. To-day there is just about half the general mortality from tuberculosis that there was then; and I am beginning to wonder whether these later records are not revealing to us what we are too blind to see: that

is, that the number of infected children *is growing smaller.*" This statement stimulated much of the large volume of tuberculin testing that has since been done and which has shown an ever decreasing incidence in tuberculous infection among children. So much so that to-day less than 5 per cent of the children of grade school age in some of our communities have been infected with tubercle bacilli.

Again Krause (6) said: "All in all, it is difficult to comprehend the logic of the frequently expressed warning that makes a sharp distinction between children and adults in respect to the dangers of exposure to tuberculous infection. . . . It would seem the better wisdom to presume not at all upon a resistance, and acquired immunity, that must be of undeterminable and hypothetical integrity in any particular case. We shall be following the larger science and come to a safer practical result if we adjudge children and adults alike before the hazards of tuberculous infection. *The only rational attitude is to protect all human beings, of whatever age, against exposure.* To allow the impression to get abroad that adults walk within a charmed circle of acquired immunity, that maturity is a privileged age, can lead only to evil, if it is accepted and acted upon. Besides, there is much evidence that it may be far from the truth."

This statement has been confirmed through actual testing; adults free from contamination with tubercle bacilli when exposed become infected in large numbers. Age apparently has little to do with the development of first-infection type of tuberculosis.

With reference to the value of the tuberculin test in diagnosis, Krause said: "Here lies one of our great opportunities in diagnosis to-day. Those of us who take life and our profession seriously, run the danger of despondency in contemplating the time wasted in striving to manufacture consumptives by all the many more or less devious or dubious methods when days and weeks previously a simple skin test or two would have proclaimed that the materials necessary for tuberculosis to wit, tubercles, do not exist. This point we might have settled within two or three days of first meeting with our patient, and then gone on to more profitable and productive 'leads' as we dismissed tuberculosis from our mind." The great value of the tuberculin test in diagnosis is much more appreciated than when Krause made this statement.

In discussing the prognosis of tuberculosis in infants, Krause said: "The more I see of tuberculosis in infants and the more I confirm diagnosis by the aid of new methods, the more tuberculous infants I find

who run along with comparatively little illness and withstand their infection well." Prior to this time it was generally held that tuberculous infection in the infant is very likely to result in death, particularly if it occurs during the first six months of life and is still a very serious matter if it occurs during the first two years of life. Actual testing of infants and young children have only confirmed Krause's observation, for it has been demonstrated beyond doubt that only a small percentage of infants and children who become infected with tubercle bacilli die or even fall ill from tuberculosis before the period of adolescence. However, there still lurks in the minds of many persons a great fear of so called "infantile" tuberculosis believed to be caused solely and directly by the first attack of tubercle bacilli upon the body. I have not seen any serious tuberculosis develop in the bodies of infants or young children except that of a reinfection type, such as meningitis, miliary disease and pneumonia. There is in the literature a number of reports in which it is stated that the first-infection is a highly fatal disease for infants of all races and adults of primitive races but I cannot recall a single reported case where there has been a careful study of the sensitization of the tissues to tuberculoprotein over a period of a few weeks or longer before illness began, and until someone has made such a careful study of a sufficiently large number of individuals, I do not see how we will be able to support the belief that deaths are due directly to the first-infection type of lesions. The fact is well established that the acute highly fatal reinfection forms of tuberculosis, which occur in infancy and early childhood, also occur in every decade of life. Therefore, it does not seem that we are justified in grouping and designating them as the "infantile" type of tuberculosis.

In discussing tuberculosis among certain races of people thought to be highly susceptible to the disease, Krause says: "And it is suggested that circumstances other than innate lack of resistance, circumstances too that are facts, may contribute toward rendering tuberculosis unusually destructive and fatal for those of low civilizations at any rate for those who come in contact with the whites of Europe and America. Judged by our standards, the common living habits of savages and semisavages are inordinately dirty. At any rate they are supremely adapted to the contracting and spread of bacterial diseases, particularly one like tuberculosis, unique among infections in that it can be contracted in every conceivable way, via every possible portal of entry, directly and through an intermediary carrier. The common bowl without individual utensils

at meals; the intimate herding at sleep; the windowless, chimneyless, never-cleaned, littered habitations, if dwellings there are; the unwashed oiled and pomaded bodies in the filthy rags if clothes are worn, must individually and together be regarded as hothouses of infection, if tubercle bacilli are loose. We cannot imagine a more fertile soil in which to spread an infection; as for tuberculosis, all that is needed is the sowing of the bacillus. And, if seed-time ever does come it will be marked by extreme dissemination and quantity of germs." This statement resulted in actual observations which have brought forth convincing evidence that excessive exposure to tubercle bacilli of the members of such races as the American Indian and the Negro are far more important from the standpoint of developing tuberculosis than any innate lack of resistance.

Just what is this latent period in tuberculosis and why has it been responsible for so much bitterness among workers and for the retardation of progress?

Dorland defines latent as "concealed; not manifest; potential." Webster defines it as "not visible or apparent; hidden; concealed." Steadman defines it as "not manifest; concealed; noting the period of incubation of an infectious disease before the appearance of the prodromal symptoms." It was this period of concealment that obscured the presence of tuberculosis in animals and men until symptoms appeared, physical signs were easily elicited, or tubercle bacilli were recovered from the excreta or secreta. It was this period which caused man to draw a sharp dividing line between infection and disease. It was this period which permitted the disease to become advanced and communicable before it was detected, and thus perpetuate itself.

While the disease was concealed or hidden and free from external manifestations in the majority of cases, it could truly be called latent according to the definition of the term because we had no way of revealing its presence until recent times. Through improved methods of examination and a better understanding of the disease, there has come about a marked decrease in the period over which the term "latent" is applicable in the sense of concealment; that is, its presence is now revealed far earlier than it was a few decades ago. Inspection of the surface of the chest, palpation, percussion, and auscultation may result in significant evidence before there are any symptoms. However, none of these phases of the examination differentiate with certainty tuberculosis from other disease of the lungs and pleura. Moreover, evidence obtained by these phases of the examination is usually that of disease

fairly well advanced. Inspection has been so extended in recent times as to bring to light a previously unseen field and, thus, has very materially limited our conception of latency as it applies to tuberculosis. For example, inspecting the sputum and gastric contents may bring to light the presence of tubercle bacilli in a progressive stage which in times past would not have been known to exist, or if so would have been considered latent. Fluoroscopic and X-ray film examination have extended inspection materially. So much so, in fact, that one is able to visualize shadows which prove to be cast by chronic reinfection type of tuberculosis two or three years before it causes symptoms. Between the time when shadows of lesions can be visualized on fluoroscopic or particularly X-ray film examination and the appearance of symptoms, serial X-ray examinations of the chest will show evidence of definite extension of disease and sometimes the appearance of cavities, which prove beyond doubt that the disease is progressive. Not infrequently, one hears the remark that a person, who has apparently been well until a pulmonary haemorrhage or an acute illness makes its appearance as the first external manifestation, must have had an old latent lesion which has suddenly flared up. In most such cases for months or even years before, X-ray films would have revealed evidence of a progressive lesion.

One unfortunate fact about shadows on the X-ray film is that on first examination they are not diagnostic. In a large series of cases for whom roentgenologists attempted to make diagnoses from the X-ray films alone, after which internists made complete examinations, of which the film was only a part, and arrived at definite diagnoses, it was found that the X-ray diagnoses were correct in approximately 50 per cent of the cases. Nevertheless, the shadow on the X-ray film is often the only evidence available as to location of a tuberculous lesion, and if serial films are made valuable information is obtained regarding the progressiveness of the disease. Thus, latency has lost its applicability over a long period of time in chronic pulmonary tuberculosis. More recently our criteria have been improved through the use of the red-cell sedimentation rate and the differential leucocyte count but we must never forget that considerable change may be taking place in a tuberculous process which will not be detected by any other single phase or a combination of all other phases of examination.

Prior to the time that chronic pulmonary tuberculosis of the reinfection type has reached such proportions as to cast shadows which can be visualized on the X-ray film or even when only the first-infection type

of tuberculosis exists, it usually is no longer concealed from the physician's detection. Indeed, the presence of tuberculosis in the body can be detected by the tuberculin test within three to seven weeks after it begins. The tuberculin test is a rather crude method of detecting allergy, since it must be present to a fairly high degree before the tissues react so as to be obvious to the naked eye. Dienes (7) has shown that the presence of allergy in low degree can be determined by microscopical examination for some time before the tissues react to tuberculin in the usual characteristic manner. By this method, the presence of the disease may be revealed within a few days after the initial tubercle formation begins. Only during the period between the focalization of tubercle bacilli and the appearance of allergy is the disease truly concealed.

A positive tuberculin reaction informs us with certainty that a primary complex is developing or has developed somewhere in the body, even though all other phases of the examination during life fail to reveal its location. Our evidence comes from good sources, namely, experimental work among small animals, large numbers of postmortem examinations of apparently healthy cattle slaughtered for no other reason than a positive tuberculin reaction, and postmortem examinations of persons who have died from other conditions. Therefore, even though we are unable to determine the exact location of the primary complex during the lifetime of many persons whose bodies contain them, we must be able to appreciate the fact that they are present as indicated by the positive tuberculin reaction. *Because we cannot locate lesions by our crude methods of examination, it does not suffice to say that they are of no significance; and because they are producing no symptoms, it does not suffice to say that they are not progressive.*

For many years, Robertson (8) collected at postmortem lesions of the primary complex. Careful examination of these lesions, together with other reported studies, led him to the following conclusions:

> Tuberculous infections may occur and pursue their entire course without demonstrable clinical phenomena, that is, without attracting attention of patient or physician to their presence.
>
> Recognized tuberculous infections may subside and be regarded throughout remaining life as healed and still remain continuously active.
>
> Apparently healed tuberculous lesions may become clinically active after varying intervals.
>
> No form of physical examination can assure any individual that he or she does not harbor the menace of active tuberculous infection.

The safest rule for physicians and patients alike is to regard tuberculosis as possessing an ever present potentiality for becoming active. One can almost say: "Once infected, always infected."

It is obvious, therefore, that no one is justified in making very definite statements about tuberculous lesions which cannot be located by examination in the bodies of persons who react positively to the tuberculin test, nor is anyone justified in making very definite statements about the primary complex when a part of its location is revealed by evidence of calcium deposits which cast shadows on the X-ray film. What is transpiring in the vicinity of the calcium deposits usually cannot be determined by X-ray examination. Evidence of a deposit of calcium in a hilum lymph node may be revealed in the X-ray examination when at the same time the node may contain large amounts of caseous material or pus which are not revealed, and yet it may rupture through the wall and disseminate large numbers of tubercle bacilli to adjacent or remote parts of the body within a few hours or a few days after the film failed to reveal its presence. Robertson says: "There is no expert, no matter what experience or special training he may have had, who has not been 'fooled' by this disease." He points out that the patient is often assured that tuberculosis is not present when it is and that the patient is told that the tuberculosis which he once had has been completely healed. "Such a statement can never be made with any great degree of certainty and it is my purpose here to emphasize this fact." Again he says: ". . . for many years my attention has been focused on those cases demonstrating the latent or dormant characteristics of the disease. This emphasis has seemed all the more justifiable, not only because of the relative frequency of such cases, but also because the recent apparent subsidence of the virulence of the tuberculosis pandemic has led to extravagant statements about its curability, thereby tending to foster a spirit of blind optimism, which the facts do not warrant."

The question arises as to whether there is a period of complete inactivity between the development of the primary disease which begins in infancy or childhood and the development of the reinfection type of disease as adolescence approaches and thereafter, except in cases in whom all bacilli die. Due to the fact that from approximately two or three to ten or eleven years of age the morbidity and mortality from pulmonary tuberculosis is low, this age period has been considered as one of inactivity of the disease. This was based somewhat upon the assumption that prac-

tically all infants have been infected with tubercle bacilli, which in reality is not true. Even in Pirquet's (9) study of children, nearly thirty years ago, many of whom were from homes where clinical tuberculosis existed and others were from poor sections of the city, the incidence of positive reactors was only 5 per cent in the first year and 80 per cent in the tenth year. Concerning this incidence of positive reactors, Pirquet says: "This high percentage cannot be considered as being the figure for all children, as very many cases are admitted into the hospitals because of tuberculosis."

In this country, in recent years, the number of infants becoming infected with tubercle bacilli has been relatively small. In many tuberculin testing surveys, the incidence of positive tuberculin reactors has been found small even at the age of eleven or twelve years. Indeed, in the high-school age period, 20 per cent is high except in a few cities, particularly Philadelphia, and in some places only approximately 5 per cent react to the test in this age period. In the city of Minneapolis, the incidence of positive reactors among grade-school children has decreased from 47.3 per cent in 1926 to approximately 17 per cent in 1936. Therefore, one reason for the low incidence of clinical disease among children to-day is that such a small percentage of them have developed the primary complex.

While it is true that a few of the children reacting positively were infected in infancy, more have been infected during the period of childhood and, therefore, the duration of time since the primary complex was established is relatively short. Except for the acute forms of reinfection type of tuberculosis, such as meningitis, miliary disease, and pneumonia, there is apparently quite a long period of time between the laying down of the primary complex and the development of reinfection forms of tuberculosis of clinical significance.

As far as the period of freedom from clinical disease is concerned during childhood and up to adolescence, there apparently is no difference in the various races of people in this country except what can be readily accounted for through excessive exposure. The American Indian, Negro, Mexican and white child apparently react in precisely the same manner to the first infection with tubercle bacilli; that is, the same defense mechanism is present and effective. Until recently we believed that the natives of Africa had been infected in very small numbers and that when first infection occurs it is a highly destructive, rapidly fatal disease. However, light was thrown on the subject (10) when approximately 93,979 native African boys were examined preliminary to or

while working in the mines and approximately 65 per cent were found to react positively to the tuberculin test. Apparently these boys had tuberculosis in a latent form as have white boys of the United States.

Observations on rather large numbers of persons who have developed the first-infection type of tuberculosis in adult life lead one to question whether the period of latency in childhood is essentially different from that of later life, since equally long periods of time exist between the laying down of the primary focus in adult life and the development of clinical reinfection type of disease. The work of Heimbeck (11) has occasionally been used to disprove this observation. From his reports it has been contended that first infection with tubercle bacilli is a much more serious matter in adult life than in childhood. On analysis of Heimbeck's table, however, it appears clear that many of the lesions he describes as having developed in the bodies of student nurses in a relatively short time after the tissues were sensitized are nothing more than parts of the primary complex or manifestations of high degree of allergy or pleurisy, such as occur also among children.

For example, in a group of ninety-four student nurses who were previously negative to the tuberculin test and who were later considered tuberculous, nineteeen showed only erythema nodosum; five, erythema nodosum and pleuritis; ten, erythema nodosum and pulmonary infection; eleven, pleuritis; eight, pleuritis and pulmonary infection; sixteen, pulmonary infection with evidence of hilum lymph node disease. Thus, sixty-nine of the ninety-four had what appears from the description as only evidence of a high degree of allergy as manifested by the presence of only erythema nodosum or first-infection type of disease in the hilum lymph nodes or pulmonary parenchyma or pleuritis, which often is an early accompaniment of the first-infection type of disease in the lung. Thus, only the twenty-five remaining students had what might be considered from the description as serious reinfection forms of tuberculosis. Three had pulmonary tuberculosis with erythema nodosum, one of whom died; two had pulmonary tuberculosis with pleuritis; sixteen had pulmonary tuberculosis, of whom six died; two had miliary tuberculosis which caused death, and one had involvement of the ribs accompanied by pulmonary infection. One must not overlook the fact that in the remaining 172 student nurses who became positive tuberculin reactors and, therefore, had primary complexes in their bodies, there were no external manifestations, nor was the location of the primary complex determined at the time the report was made.

Thus, it appears that regardless of the age in life when tubercle bacilli

attack the body, there is usually no evidence of a chronic form of clinical disease over a long period of time, at least, many months and more often many years or even decades. *Indeed, there is nothing more spectacular in the whole realm of disease than the ability of the human body to control tubercle bacilli when they first make their attack, regardless of such factors as age, race, nationality, and home conditions.*

There is no convincing evidence to show that the so called latent period of tuberculosis in childhood is an "immunosatoric latency" since the defense mechanism of the body which attacks the tubercle bacilli of first infection is almost identical with that which attacks inanimate objects of the particulate type; both are locked up in the pulmonary parenchyma and the regional lymph nodes. If the immediate control of tubercle bacilli is due to a specific immunity, one would have to assume that such an immunity is in operation against the inanimate object. The only significant difference lies in the subsequent possibilities and this difference is due to the fact that the bacilli are alive and capable of multiplying and even gaining freedom. *The long period of time that is required for tuberculosis to develop into clinical disease in the human body probably is responsible more than anything else for the absence of symptoms and illness during the period of childhood to adolescence.*

The question has frequently come to my mind as to whether we have correctly interpreted Koch's phenomenon with reference to tuberculosis in the human body; that is, whether our translation of what is seen in the animal is understandable in terms of human experience. When tubercle bacilli are introduced into the body of an animal many of them are quickly carried to lymph nodes where they are imprisoned, but in much of the experimental work such large numbers of bacilli are introduced that the defense mechanism is overwhelmed; that is, there are not enough defense elements to lock up all of the tubercle bacilli before allergy develops to a high degree and those which are not controlled by this time are free to produce very intense reactions, necrosis, and death of the animal.

Meyer (1) says: "The micro-biologist, who intentionally administers huge doses of micro-organisms in order to decide the pathogenicity of a disease agent for certain animals, has doubtless drawn and continues to draw erroneous conclusions. Fortunately, in recent years it has been appreciated that the massive infections, only too often supplemented by procedures which paralyze and deaden the resistance, have in no way imitated the natural conditions."

Apparently such a condition as that produced in the animal is a rarity in the human body for certainly the older opinions have not held up under the actual observations of the last decade. The belief that the first infection with tubercle bacilli is an asset to the animal or human body as derived from the usual interpretation of Koch's phenomenon is based upon the fact that the tissues have been so changed by the presence of the first infection in the body that when tubercle bacilli of reinfection, whether from exogenous or endogenous sources, come in contact with them they are met by a much more intense outpouring of neutrophiles and in due time other leucocytes, so that bacilli are fixed at the site of lodgment and very few escape to the regional lymph nodes. Therefore, when bacilli in sufficient number are introduced into the skin of a previously infected animal there occurs necrosis and abscess formation which becomes a chronic process and later fibrous tissue is laid down in the lesion. However, not all bacilli necessarily perish in such a lesion. This development may appear to approach the ideal from the standpoint of a skin lesion but what is to be our interpretation when it occurs in such organs as the lungs which in human experience is probably the most common location. Here the intense reaction frequently leads to necrosis, as in the skin, the necrotic tissue is often eliminated through a bronchus and a cavity remains in the lung. Everyone knows that this is likely to be a desperate situation, not only from the standpoint of prognosis but also from the standpoint of the patient's human associates, so much so that in therapy serious efforts are made to obliterate such cavities at the earliest possible moment. In my experience, such a desperate situation developing in a first infection lesion is a myth.[4]

Tuberculosis is not a serious problem to the farmer as far as the calves and young cattle are concerned, yet in times past the tuberculin test revealed the fact that many of them had the disease. It was not until later life that the animals fell ill and died on the farm. In fact, during the year 1916, at all points under Federal inspection, the carcasses of enough cattle were condemned because of tuberculosis to fill a solid train 11.8 miles long (12). A large porportion of these condemned carcasses were older animals.

Tuberculosis among swine was not recognized as a serious problem to the farmer until the United States Bureau of Animal Industry began

[4] Ghon (Der primäre Lungenherd bei der Tuberkulose der Kinder, Berlin, 1912) reported the autopsy findings of 170 children up to fourteen years of age in whom a primary pulmonary focus could be identified. In 57 (33.5 per cent) the primary focus was excavated. [Editor]

inspecting the carcasses of hogs at the slaughter house. Then organs were found to be definitely tuberculous in these animals that had been fattened for the market and appeared in perfect health. During the year 1916, at all points under Federal inspection, there were condemned because of tuberculosis enough hogs to fill a solid train 8.6 miles long. The same year the carcasses of enough cattle and hogs were sterilized because of tuberculosis and the meat sold at approximately one-half the usual price to fill a solid train fourteen miles long. In recent years the tuberculin test has revealed the fact that it is not uncommon to find as many as 25 per cent of the animals in swine herds contaminated with tubercle bacilli. The only reason this disease was not previously considered a serious problem by the farmers is that most swine are marketed in early life; they do not live long enough for the disease to cause sufficient destruction in organs to make them ill.

In recent years, tuberculosis among barnyard fowls has been discovered to be a serious disease. One large packing concern found that the losses were so great through the condemnation by the inspectors that it was more profitable to purchase chickens in distant states where tuberculosis did not exist among them. However, the loss to the local farmers resulted in an investigation to find a method of control which would make the chickens they raised suitable for the market. It was learned that among chickens, even though the disease is present extremely early in life, it rarely reaches such proportions as to cause illness or death or to be communicable to others until after the age of eighteen months. Aside from destroying the tubercle bacilli which already contaminated the soil of the yards, the problem was easy to solve; it simply consisted of disposing of all chickens that had reached the age of eighteen months. Fortunately, the most productive period in the chicken's life is before eighteen months of age. Now the tuberculin test reveals the presence of tuberculosis, even in chickens, soon after the primary disease begins to develop.

As in animals, it is also true in the human family that the disease becomes most destructive as adult life approaches and thereafter. In 1925 Krause said: "As it works out in life, it is beyond dispute that the ravages of tuberculosis are in every way greater in later life than in childhood." He estimated that for the upper age group there is annually one death for every 170 persons infected, while in childhood, there is only one death for every 800 infections. Chadwick (13) has reported that among grade-school children he has found only one child in each

3,300 examined to have reinfection or adult-type tuberculosis. In our studies at Lymanhurst, we found only one such child in each 2,016 examinations (14).

The period of latency in tuberculosis does not end with the beginning of adolescence in the majority of human beings who develop the first-infection type of disease. Latency continues in the bodies of many persons and even animals throughout the span of life. Among our group of children with positive tuberculin reactions, approximately 10 per cent developed the reinfection type of disease and were ill or dead by the time the majority was or should have been reached. If the morbidity continues at the same rate or is even somewhat retarded, at least 20 per cent of these children will fall ill before they have lived out the span of life. Many of the remainder will continue to carry their latent or smouldering disease.

In the past few years, the fact has been well established that persons in any age period of life may develop clinical tuberculosis. A few years ago we said that those who were destined to develop clinical pulmonary disease would show some evidence of it on the X-ray film by the time the high-school age period was completed. We later raised that age to approximately twenty-four or twenty-five years. We are now forced to raise it to the end of life. I have recently seen two women who illustrate this point. One is thirty-one years, who in 1934 was carefully examined and X-ray films revealed no evidence of disease in either lung. However, in 1936 films showed small shadows in the left upper lobe which have continued to increase in size, until she had tubercle bacilli in the sputum. The other is a woman of forty-seven years, who in 1934 was carefully examined because her only son, an adult of twenty-eight, fell ill from tuberculosis which apparently was contracted outside the family. The mother's examination at that time revealed no evidence whatsoever of disease in either lung. However, in 1936 there was evidence of very definite tuberculosis in the left upper lobe, the sputum was positive, and the disease was definitely progressive. Similar cases have been described elsewhere (15). Therefore, we must not limit our discussions of the period of latency to childhood. *As long as we allow communicable cases of tuberculosis to remain in our communities, smouldering disease will develop among the contacts regardless of age and as long as smouldering tuberculosis is allowed to develop in the bodies of human beings, we will have a morbidity and a mortality from this disease, regardless of age.*

The latent or smouldering stage of tuberculosis is very seriously con-

sidered by the veterinarians. Many years ago a government committee in a report on Location of Tuberculosis in Cattle (16) said: "When the tuberculin test is applied to cattle for any purpose it should be clearly understood that the reacting animals are to be regarded in every sense of the word as recognized cases of tuberculosis, which under an obligatory notification law, must be reported at once to the proper authority." The veterinarians even slaughter all healthy appearing cattle found to have tuberculosis by means of the tuberculin test because they have no method of treating it. They recommend that all chickens infected with tubercle bacilli be disposed of when or before they reach the age of eighteen months, in order to prevent the spread of disease to others and great loss among those which fall ill.

Only recently we have come to consider seriously the potentialities of smouldering tuberculosis during the period of childhood. At one time we even looked upon the presence of this disease in the body of a child as an asset because we thought it to be a valuable immunizing agent. Now we know that once the primary complex has been allowed to develop, as manifested by a positive tuberculin reaction, there is no treatment of any avail; that is, the condition is beyond recall. Immunity does not develop sufficient to destroy the tubercle bacilli. No treatment that we know, such as long periods of strict bed-rest or even collapse therapy, destroys the tubercle bacilli in the lesions of the primary complex. Moreover, we have no practical method of permanently desensitizing the tissues of such persons.

Our problem is no less significant than that of the veterinarian but where he solves it at once we must wait for further developments; that is, we must keep close watch for the development of the destructive type of disease so that if and when it occurs, treatment may be instituted before it becomes communicable or causes illness.

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MULTIPLE CALCIFICATIONS IN THE SPLEEN

With Report of a Case

LEWIS J. MOORMAN

Haematogenous tuberculosis in the human organism is of much more frequent occurrence than commonly recognized. Miller (1), after reviewing the French and German literature, and calling attention to the long-standing recognition of this condition, with its varied clinical and pathological manifestations, particularly by French clinicians, makes the following statement: "As a result of this work it is possible now to arrange the vast polymorphism of tuberculosis in an easily reviewable order, showing the range of clinicopathological conditions from the simple abortive primary complex, through mild and increasingly severe, to overwhelming generalization, and from mild abortive apical lung lesions to hyperacute extensive multilobar localizing processes."

Recognition of the frequency of haematogenous tuberculosis, with its wide range of pathological possibilities, is of great significance in connection with any study of splenic pathology. The strategic position of the spleen places it in line for the haematogenous overflow, not only in connection with the primary complex, but for the successive showers of tubercle bacilli accompanying the not uncommon recurrent blood-stream disseminations arising through caseating tracheobronchial or mesenteric lymph nodes.

Krause (2), in his studies on tuberculous infection, found tubercle bacilli in the spleen of guinea pigs four days after subcutaneous inguinal inoculation. With these facts in mind, it is not surprising that tuberculosis of the spleen is a common postmortem observation, particularly in those who have died of tuberculosis or who have presented clinical manifestations of the disease during life.

Calmette (3) states that in almost all grave forms of tuberculosis, "the spleen is involved to a greater or lesser degree by the tuberculous process. The tubercles remain as a rule very small, tend toward fibrosis and are usually overlooked at autopsy."

In the report of his work on "The Primary Lung Focus of Tuberculosis in Children," Ghon (4) details the postmortem findings in 125 children.

He found tuberculosis of the spleen in 55 cases, tuberculous perisplenitis in three, and a tuberculous lymph node at the hilum in one. Counting only the 55 cases of *bona-fide* tuberculosis of the spleen, we have an incidence of 40.4 per cent in tuberculous children.

The clinicopathological medley referred to by Miller as the polymorphism of tuberculosis is, in all probability, due to the ever-present contest between the intangible forces which have to do with the progression and retrogression of tuberculosis. According to Sweany (5), the most retrogressive process in the course of tuberculosis is calcification.

Calmette (3) believes "the spleen certainly plays a very important protective rôle against tuberculous infection." He refers to the work of Arloing, showing that if the spleen were removed before the intravenous injection of tubercle bacilli in animals, tuberculous lesions progressed much more rapidly to caseation than if the spleen were removed after intravenous injection.

Foot (6) and Lewis and Margot (7), working respectively with rabbits and mice, failed to confirm the findings of Arloing. However, Marmorston (8), working with mice, repeated the experiments of Foot, Lewis and Margot, with striking evidence of lowered resistance to tubercle bacilli in the splenectomized mice; thus apparently confirming the work of Arloing.

Lurie (9), studying the fate of tubercle bacilli injected intravenously into rabbits, concludes that of all organs in the body, the spleen possesses the maximum phagocytic capacity for tubercle bacilli. He also observed that after twenty-four hours, the spleen had retained more tubercle bacilli than any other organ in the body. This observation is in keeping with Krause's (2) conclusion that under ordinary conditions the spleen is the most extensive depot of tubercle bacilli in the guinea pig.

Granting that the spleen possesses exceptional protective forces which operate through the rapid destruction of the tubercle bacilli, and through the tendency toward ready resolution of tubercle when it occurs, we know that demonstrable tuberculosis of the spleen is not uncommon. In such cases, the infection is often overwhelming with progressive, destructive lesions. However, it seems reasonable that the spleen, with its relatively high resistance to tubercle bacilli, should frequently manifest retrogressive phenomena, including calcification.

Medical literature is peculiarly silent with reference to calcification of the spleen. It is briefly discussed in many of the textbooks on pathology and pathologists generally agree that it is not an uncommon post-

mortem finding. With consensus of opinion as to its relative frequency, it is disconcerting to find there is no uniformity of opinion among pathologists as to the course and nature of the multiple, small and medium sized calcified nodes so frequently found in the spleen. In many cases there seems to be no definite way to differentiate between phleboliths and healed tuberculosis or between these and other probable causes of tissue death and the laying down of calcium. No doubt all will agree with Krause—"It is probably true that the most common sites of calcific deposit are those where there has been tissue death caused by the tubercle bacillus. And this, in my opinion, is only for the reason that the tubercle bacillus has been, far and away, the most common cause of focal tissue death, and especially most common in instances in which foci of disease may arise unknown and run a completely unsuspected course."

Henke and Lubarsch (10), discussing calcification of the spleen, refer to the calcification of thrombi (venous stones or phleboliths) and report a case with illustrations showing a spleen containing numerous calcified nodes which appear to be identical with those found in the author's case and in other cases known to be tuberculous in origin.

During the past few years the literature has contained several reports of accidental discovery by X-ray of calcification of the spleen through routine diagnostic X-ray service. Here we find the same difficulty in making a diagnosis. Koppenstein (11), who receives credit for the first X-ray reports on calcification of the spleen in 1927, gives an account of eight cases with X-ray pictures. He considers all of them due to phleboliths and while he presents a rather plausible argument, he does not produce convincing evidence of venous origin.

In 1928 Courtin and Duken (12) reported three cases of tuberculosis in children with discovery by X-ray of multiple calcified nodes in the spleen. All of these cases had demonstrable destructive tuberculous lesions in other parts of the body. In one it was possible to note, by serial X-rays, progressive calcification in the spleen. The authors refer to the cases reported by Koppenstein and suggest the possibility of mistaken diagnosis. They call attention to the similarity of the cases as shown by X-ray and refer to the fact that some of Koppenstein's cases also had pulmonary lesions.

Rudisill (13), in 1932, reported four cases discovered by X-ray in the routine X-ray examination of approximately 350 cases. The calcifications were considered phleboliths because they were apparently of the

same type as the phleboliths found so often in the pelvic circle. He also considered the absence of clinical manifestations, the type, and distribution of the calcifications, as being indicative of phleboliths. However, in one case there was evidence of healed bilateral apical tuberculosis; in two the chest was considered negative and in one the chest was not examined.

In 1933, Shands (14) reported three cases of so called primary tuberculosis of the spleen with a preoperative X-ray diagnosis based upon the finding of calcified nodes in the spleen. After surgical removal all were proved to be of tuberculous origin. In one, bacilli of the bovine type were reported and it was found that the X-ray in this particular case revealed the presence of a calcified mesenteric lymph node. In addition to the above published cases, one case has been reported by each of the following: Teschendorf (15), Polgar and Szemzo (16), Bunch (17), Spitz (18), Miller (1), and Beck.

This review of the literature discovered reports of twenty-four cases of calcified nodes in the spleen observed during life by X-ray. Of these, twelve were diagnosed as phelboliths and twelve as representing calcified tubercles. Eight of those diagnosed phleboliths were reported by Koppenstein (11) and the diagnosis was questioned by Courtin and Duken (12). It is significant that practically all the cases reported as being due to tuberculosis were proved by laboratory studies after splenectomy, or at autopsy. The cases reported as phleboliths were so considered because of size, number, distribution, and configuration. It has been shown that the X-ray portrayal of nodes, later proved to be of tuberculous origin, is, in every respect, similar to those reported as phleboliths.

In a review of the literature we are impressed with the recurring differences of opinion. The weight of evidence seems to be in favor of tuberculosis, since in many of the cases so diagnosed it has been possible to demonstrate the presence of tuberculosis, not only in other organs of the body, but in the spleen, by the discovery of specific tissue changes or the presence of tubercle bacilli after surgical removal or at autopsy.

It is obvious that a large number of cases of calcification of the spleen have been discovered during life through the routine work of large X-ray services. With the usual exposure for chest or abdominal pictures, calcified nodes in the spleen may not appear in the X-ray film unless the spleen is clearly shown through a gas bubble in the stomach or in the splenic flexure of the colon. Dr. Henry C. Sweany, referring to work yet unpublished, reports calcified nodes, discovered by postmortem X-

raying of the spleen, in 24.6 per cent of all cases dying in the Chicago Municipal Tuberculosis Sanitarium. However, a review of the literature indicates that surprisingly few cases have been reported and that the relatively frequent occurrence of this condition is not generally known.

Case Report

J. C. A., a practicing physician, age 53. Past history: essentially negative, except that in 1914, when 31 years of age, he developed symptoms of a low-grade toxaemia with undue fatigue and a slight daily rise of temperature as predominant features. The author was consulted and because of the persistent toxaemia and the constant presence of a few fine crackling râles at the right apex, a diagnosis of minimal pulmonary tuberculosis was made. The symptoms persisted for a period of one and one-half to two years. There was also a complaint of pain in the lumbar region and under the lower ribs, which was more noticeable in the presence of general fatigue. In 1915 the patient was examined at the Mayo Clinic. A recent review of the record at the Mayo Clinic by Dr. W. S. Lemon resulted in the following report: "X-ray of the chest negative; physical examination negative. Apparently his trouble consisted mainly of aching pain in the lumbar region."

In 1926 a posterior gastroenterostomy was performed at the Mayo Clinic because of duodenal ulcer. The last examination at the Mayo Clinic was in 1932. An X-ray of the chest at this time was considered negative with reference to the lungs; however it did show calcification of the arch of the aorta. Doctor Lemon's report indicates that—"There was nothing reported in any of the X-rays relative to calcification of the spleen." Neither were they able to find clinical evidence of tuberculous infection at any of the examinations.

Family history: Of eleven brothers and sisters, three died in infancy of unknown cause. One sister died of adenocarcinoma and a brother died of Hodgkin's disease. Otherwise the family history is of no interest.

The patient gave a history of having been in usual health until March 25, 1936, when he went to bed because of a "head cold, slight cough and fever." The continuation of these symptoms with occasional chilly sensations caused him to suspect influenza. After ten days in bed he was up attending to his professional duties for a period of several days. Because of persistent symptoms with progressive weakness, increasing cough and expectoration, he gave up his work and remained in bed.

On April 19, nearly one month after onset of the present illness, the patient was seen by his colleague, Dr. H. M. McClure, who supplied the following data. The patient is a well nourished male about six feet tall, weighing approximately 185 pounds. His skin is pale and moist. Examination of head, face and neck essentially reveal nothing of note. His cardiovascular system appears to be normal. Examination with reference to the respiratory

system revealed limited excursion of the upper right, diminished tactile fremitus, pronounced dulness with marked limitation of breath sounds over the upper right. The temperature was ranging from 99° to 100°F., the pulse rate was moderately accelerated. The tenacious mucoid sputum was streaked with blood.

X-rays of the chest were interpreted as follows: Flat film made May 2, 1936; right thorax; hilum completely fused with diffuse ground-glass opacity extending from the level of the third interspace to apex with definite evidence of a cavity in the second interspace near the periphery, 1 x 1½ inches in diameter. The lower margin of the above described opacity is sharply defined and possibly represents demarcation by interlobar fissure. The lung field below this line is fairly clear with the exception of slight exaggeration of tracings and a few calcified or partially calcified nodes. The diaphragm is apparently normal. The left thorax shows a moderately heavy hilum with no definite infiltration in the parenchyma. Cardiovascular shadows are normal.

Serial X-rays dating from May 2, 1936 to June 16, 1936 show progressive destruction of lung tissue in the right upper lobe with the ultimate formation of multiple cavities. A blood count was reported as follows: total white count 16,700; red cells 4,570,000; haemoglobin 70 per cent. The treatment was symptomatic.

On May 12 the patient had a severe attack of coughing, accompanied by the expectoration of quantities of odorless yellow purulent material. Because of persistent distressing cough with free expectoration, artificial pneumothorax was instituted. Within a period of five days approximately 1,200 cc. of air were given with marked reduction in cough and expectoration. Refills were continued at weekly intervals. There was rapid loss of weight with cachectic manifestations, including pronounced muscular weakness. A diagnosis of malignancy of the right lung was made at this time.

The author was called to see the patient in consultation with Doctor McClure on June 20. Examination confirmed the above described clinical course and elicited physical signs in keeping with the pathological conditions observed by Doctor McClure and shown in serial X-ray films of the thorax. The diagnosis of intrathoracic malignancy with secondary pneumonitis, multiple abscesses and cavity formation in the upper lobe of the right lung was concurred in. Bronchogenic carcinoma with partial occlusion of the right upper lobe bronchus was considered the most probable pathological entity. On June 29, following the sudden onset of sharp pain in the right thorax, accompanied by the symptoms of shock, the patient expired. Spontaneous pneumothorax was suspected.

While inspecting the serial X-ray films, attention was called to numerous small opaque oval and round shadows below the left diaphragm. Upon the discovery of these shadows the author naturally thought of

healed tuberculosis of the spleen, dating back twenty-two years to the period of persistent toxaemia, apparently due to minimal pulmonary tuberculosis.

An autopsy was performed by Doctor McClure, whose report contained the following pertinent facts: Upon opening the thorax, the right lung was found to be partially collapsed, the upper lobe being attached to the chest-wall by diffuse fibrous adhesions. Purulent material was pouring through a rent in the visceral pleura and the right pleural sac contained about 2,000 cc. of purulent fluid. The upper lobe of the right lung was adherent to the chest-wall and showed multiple cavities interspersed with hard nodular masses, attributed to new-growth. The mediastinum was fixed and all mediastinal structures were fused with the dense nodular new-growth. The left lung was apparently normal with the exception of a few scarred areas attributed to healed tuberculosis.

The abdominal organs were apparently normal with the following exceptions: The stomach showed a successful posterior gastroenterostomy. On the posterior wall of the duodenum, near the pylorus, it was possible to demonstrate a scar suggesting a healed duodenal ulcer. The spleen was free of adhesions and apparently normal in position and size, but careful examination revealed the presence of oval and round calcified nodes. The diagnosis based upon the gross pathological findings was: (1) carcinoma, originating in the right primary bronchus; (2) healed tuberculosis of the lungs and spleen; (3) healed duodenal ulcer.

Dr. Hugh Jeter examined a section from the right lung and primary bronchus, a lymph node from the mediastinum and the spleen. His report indicated that the intrathoracic new-growth was due to lymphosarcoma and that the calcified nodes in the spleen were due to healed tuberculosis, though no specific tissue could be found. Other reports were as follows: Dr. L. A. Turley, Professor of Pathology, University of Oklahoma School of Medicine, reported no specific tissue. Dr. Max Pinner, Principle Diagnostic Pathologist, Department of Health, Division of Tuberculosis for the State of New York, summarized his report as follows: "These calcified nodules do not show any remnant of specific tissue, but I do not know of any process that is likely to produce such nodules but tuberculosis." A pathological report from the Massachusetts General Hospital (Johnson and Mallory) offers this comment: "One section contains a small nodule in which and adjacent to which there is no specific tissue change. The findings are consistent with healed tuberculosis."

Dr. Henry C. Sweany, Medical Director of Research, the City of Chicago Municipal Tuberculosis Sanitarium, who has made exhaustive studies of calcification in tuberculosis, makes the following report: "A nodular tubercle with

dense capsule of hyalinized connective tissue, calcified in certain places almost to the outer border. On two sides there are broad bands of fibro-osteoid and osteoid tissue involving half the inner side of the capsule, along the margin of calcification. Estimated age at 25 years."

In the light of the history, the clinical picture and the pathological findings in this case, it seems reasonable to attribute the presence of calcified nodes in the spleen to healed tuberculosis, and to suspect that the persistent backache, associated with the febrile course twenty-two years before the death of the patient, was due to tuberculosis of the spleen.

A review of the records and a study of X-rays at the University Hospital, Oklahoma City, for a period of five years, revealed three cases of

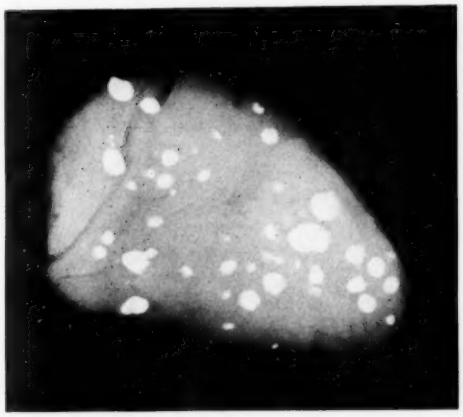

Fig. 1. Postmortem X-ray of spleen showing 56 calcified nodes

calcification of the spleen discovered by X-ray, but not reported. In one of these presenting splenomegaly with multiple calcified nodes, the spleen was removed and found to be tuberculous. In one, a man 52, death resulted from a condition attributed to syphilis of the central nervous system, though the usual diagnostic laboratory tests proved negative. A postmortem examination revealed three calcified nodes in the spleen the size of a small cherry. Laboratory studies revealed no specific tissue. The third case, a female age 66, was dismissed with a diagnosis of "generalized abdominal carcinomatosis" and could not be traced.

Since the above data were assembled, the author has discovered, through routine X-ray studies of the thorax, a case of multiple calcified

nodes associated with calcification of the splenic artery, in a woman 73 years of age. This patient presents the clinical picture of chronic pulmonary tuberculosis with X-ray evidence of moderate fibrosis and calcification in the lungs.

The author's two cases, plus the three cases found by searching the records at the University Hospital, added to the 24 cases found in the literature, make 29.

Among other conditions leading to calcification in the spleen, the following have been discovered by X-ray and reported. Walters (19) reports a cyst of the spleen with calcification of the cyst wall. Mount and Hunter (20) report a case of massive calcification apparently resulting from trauma. Kadrnka and Babaiantz (21) report three cases of calcified infarcts observed by X-ray which are so diagnosed because of their triangular shape, anatomical position and relationship, and the lack of homogeneous opacity. Heatley (22) has reported a case of calcification of the splenic artery discovered in a routine X-ray study of the genitourinary tract. The patient was a woman 72 years of age, and she had worn a drainage tube three years because of a traumatic injury to the abdomen when she was twenty-three. It was thought that the spiral X-ray shadow might be due to the retained drainage tube. Exploratory operation revealed calcification of the splenic artery. Doctor Heatley has since observed six cases with similar X-ray findings.

CONCLUSIONS

Accumulated data seem to warrant careful consideration of the following facts:

(1) The frequency of haematogenous tuberculosis and the importance of recognizing the varied pathological possibilities accompanying this condition.

(2) The common occurrence of tuberculosis of the spleen.

(3) The frequent finding of calcified nodes of undetermined pathogenesis in the spleen at autopsy.

(4) The more recent discovery of these nodes in the spleen during life in routine X-ray examinations which include the splenic region, particularly X-rays of the thorax, the gastrointestinal and the genitourinary tracts, and the spine.

(5) The limited number of reported cases and the lack of general knowledge concerning the presence of such calcified nodes.

(6) The cases discovered by X-ray during life, and having splenectomy, or coming to autopsy have, with few exceptions, proved to be of tuberculous origin.

(7) The wide difference of opinion as to pathogenesis and the desirability of concerted effort on the part of clinicians, those in charge of X-ray services, and the general pathologists, in an attempt to determine the clinical and pathological significance and to encourage reporting of cases with all available accumulated data.

(8) Other reported cases of calcification of the spleen observed by X-ray during life, and obviously not due to tuberculosis or phleboliths, have been discussed.

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AN EVALUATION OF ARTIFICIAL HYPERPYREXIA IN TUBERCULOSIS[1]

G. R. DUNCAN[2] AND E. S. MARIETTE[3]

EXPERIMENTAL DATA ON TUBERCLE BACILLI, GUINEA PIGS AND PULMONARY TEMPERATURES

This is an attempt to correlate the reasons for the belief that hyperpyrexia will have some value in the treatment of tuberculosis, with the results of experimental studies and the results of treatment of pulmonary tuberculosis by artificially induced fever.

The work on the thermolability of the tubercle bacillus was begun by us in 1932 in the hope that something would be discovered which might be of some value in the treatment of tuberculosis. The point of view during the study has been primarily that of the effect of heat on the tubercle bacillus rather than the effect of heat upon the resistance of the patient. This was based on the fact that in diseases other than tuberculosis the value of the treatment has depended on the thermolability of the organism rather than the immune response of the host.

Historically the use of elevated temperatures in the treatment of disease had its origin long before the Christian era. Max Schottelus in 1891 mentioned the protective value of fever and speaks of the Papyrus of Ebers in which the Egyptian medical men were forbidden to give medicine in febrile cases until the fourth day (1). Homer has mentioned the benign action of baths. Hippocrates (460 B.C.) knew and mentioned the favorable action of fever. The Roman baths are, of course, well known. Neymann (2) states that "the ancient Jews, Egyptians, and Chinese, advocated hot bathing and even aboriginal tribes such as the American Indians, the Negroes of tropical Africa and the Japanese used hot baths in the treatment of acute and chronic infections often with excellent results." The Kusatsu baths of Japan in use in the 17th

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Century are of interest. According to Leonard Hill (1907) the bath temperatures were between 113° and 128°F. and five baths a day and a total of 120 baths were given. Semimilitary discipline had to be used because the procedure was so arduous (3). Chronic conditions including chest ailments have been treated with these baths (4). Wagner Von Jauregg, in 1918, used malaria in the treatment of syphilis and this treatment was carried further by Kyrle who reported his results in 1924. The thermolability of *Treponema pallidum* (5) (6) and the gonococcus (7) has been shown.

Diseases now usually treated by artificial hyperpyrexia are syphilis (8), gonorrhoea (9) (10), infectious arthritis (11), asthma (12), chorea (13), etc. Tuberculosis has been considered a contraindication to treatment (14). Malaria (4), typhoid vaccine (15), rat bite fever (16), baths (17), general diathermy (18), radiatherm (19) and cabinet methods (20) (10) have been used to induce fever artificially. We have attempted to treat pulmonary tuberculosis in man by artificial fever produced by baths, general diathermy, the cabinet method, hot moist air inhalations and the radiotherm. The latter two methods will be reported on later.

The basis for the belief that hyperpyrexia is of some value in the treatment of tuberculosis is the definite relationship between the type of tubercle bacillus which causes progressive disease in domestic animals and the normal body temperatures of the latter. That is, as the range of normal body temperature increases from man and guinea pigs to the other mammals and finally to birds, the susceptibility to infection changes from the human to the bovine and finally to the avian type of tubercle bacillus(21).

Conversely, the shift from type to type is not so marked. In spite of reports in the literature that the avian tubercle bacillus may infect man, proof that such infection occurs is still lacking. Avian infections in the guinea pigs have been produced and the susceptibility of rabbits, calves and pigs to this type of tubercle bacillus is well known.

The following experiments on the "nongrowth point" of the three types of tubercle bacilli have been reported in detail elsewhere (21). In this study, twelve strains of tubercle bacilli, five human, five bovine and two avian were grown on modified Herrold's egg medium. After becoming visible to the naked eye each strain was incubated continuously for four weeks at temperatures ranging from 96° to 110°F. The amount of growth was determined by comparing the photographs of the cultures before and after incubation. According to the following tabulation, it

is evident that there is a definite correlation between the temperature at which bacilli grow *in vitro* and the temperature of the domestic animal in which that particular type of organism produces progressive disease, nonprogressive disease or no disease. It appears evident that the pos-

	TEMPERATURE							
	96°	98°	100°	102°	104°	106°	108°	110°
Human	L	L	L	P	P	O	O	O
Bovine	L	L	L	L	L	P	P	O
Avian	L	L	L	L	L	L	L	P

L = luxuriant growth; P = poor growth.

sibility of the beneficial effect of artificial hyperpyrexia is greater when the infection is due to the human type of tubercle bacillus than when it is due to the bovine or avian types.

The three-weeks thermal death point of the human tubercle bacillus has also been studied and reported elsewhere (21). Two strains of human tubercle bacilli were cultured and then incubated for three weeks at 106°, 108° and 110°F. Guinea pigs were then inoculated with 1 mgm. from each culture and autopsied at the end of six weeks. The pigs inoculated with material from cultures maintained at 106° showed extensive generalized tuberculosis, those inoculated with material from cultures heated at 108° showed moderate tuberculosis of the lymph nodes, spleen and liver, but no disease could be discovered in the lungs either upon gross or microscopical examination. The guinea pigs inoculated with material from cultures heated at 110°F. were entirely free from the disease. Thus it is apparent that heating human tubercle bacilli for three weeks at 106° does not affect their virulence while heating them for three weeks at 108° attenuates them, and they are killed when heated at 110°F. for three weeks. From this we can conclude that the three-weeks thermal death point for the human tubercle bacillus is somewhere between 108° and 110°F., a condition which it is impossible even to approximate in a human being.

We next attempted to determine what effect, if any, temperatures comparable in period of time and degree to that considered ideal in hyperpyrexia treatments would have on the growth of the human tubercle bacilli. The results are as follows:

TEMPERATURE AND TIME	COMPARABLE HYPERPYREXIA TREATMENT	AMOUNT OF GROWTH
98°F.	Control experiment	Luxuriant
102°F. for 1 hour once a week	Bath	Luxuriant
104°F. for 4 hours biweekly	General diathermy	Luxuriant
106°F. for 5 hours once a week	Cabinet	Luxuriant

From this experiment it is apparent that temperatures in degrees and for periods of time feasible for clinical application have no inhibitory effect on the growth of the tubercle bacilli.

As the maximum duration of hyperpyrexia treatments is five hours, we next attempted to determine the approximate five-hour thermal death point and thermal "nongrowth point" of the human tubercle bacillus.

Twelve cultures each of two strains of the human tubercle bacilli of known virulence were subjected to the following temperatures: three cultures which served as controls were incubated at 98°, three others were incubated at 120°, three at 130° and three at 140°F. for five hours after the tubes had reached the incubation temperatures. The tubes were then all returned to the 98°F. incubators and incubated for three weeks. The organisms which had been heated at 120° for five hours grew moderately well while those which were heated at 130° and 140° did not grow at all. Apparently then, the five-hour "nongrowth point" of tubercle bacilli is somewhere between 120° and 130°F.

In order to determine whether there was anycorre lation between the five-hour "nongrowth point" and the five-hour thermal death point, eight guinea pigs were injected intraperitoneally with 1 mgm. of tubercle bacilli obtained from the cultures after they had been subjected to the temperatures noted above. The results were as follows:

STRAIN	98°	120°	130° and 140°
I	Died of massive tuberculosis	Slight tuberculosis	No evidence of tuberculosis after 44 days
II	Massive tuberculosis at the end of 44 days	Moderate tuberculosis	No evidence of tuberculosis after 44 days

The five-hour thermal death point is somewhere between 120° and 130°F.

From these experiments it is apparent that the five-hour thermal death point and thermal "nongrowth point" of the human tubercle bacillus are far above temperatures tolerated by man.

We next attempted to determine the value, if any, of hyperpyrexia in the treatment of tuberculous guinea pigs. Twelve guinea pigs were tested intracutaneously with 0.5 mgm. of Saranac Lake Old Tuberculin and were found to be tuberculin-negative at the end of 48 hours. They were then given approximately 1 mgm. of R1 intraperitoneally. Twenty-six days later these animals were again tested with tuberculin and eleven were found to be definitely positive while one was still negative. The animals were then injected with approximately 0.5 mgm. of a strain of virulent human tubercle bacilli isolated from a patient by guinea-pig inoculation. Six of the animals were used as controls and the other six

TABLE 1

Results of artificial hyperpyrexia treatments on guinea pigs with a secondary infection of human tubercle bacilli

HEAT TREATMENTS					CONTROLS			
Number	Time*	Killed or died	Number of treatments	Extent of tuberculosis	Number	Time*	Killed or died	Extent of tuberculosis
	days					*days*		
42	23	D	3	Massive	39	46	D	Massive (pneumococcus peritonitis)
36	34	D	4	Slight (bronchopneumonic)	37	39	K	Massive
46	48	D	6	Massive (miliary)	43	48	D	Massive
44	63	D	9	Massive	41	69	K	Moderate
38	60	K	10	Moderate (abscess chest wall)	45	69	K	Moderate
40	69	K	10	Moderate	47	69	K	Moderate

* Time from the injection of the virulent strain.

including the animal which was still tuberculin-negative following injection with R1 were heated for four or five hours once a week for ten treatments. During these treatments their rectal temperatures were maintained between 104° and 105°F. save occasionally when one might become too debilitated and the treatment had to be discontinued for a while. Because guinea pigs do not perspire to any appreciable extent, dry heat in a small cabinet was used. This was sufficient to produce easily the desired fever. Due to the loss of fluid dripping from the nose, saline was replaced subcutaneously twice during each treatment, and smaller amounts were given to the controls at the same time. The results of the treatment are shown in table 1. The surviving animals formed so small a group that they were killed about two months after the treatments

began. All showed gross evidence of tuberculosis. The spontaneous deaths were somewhat more numerous in the treated group and the extent of tuberculous disease was about the same in both groups. Microscopical sections of the liver, spleen, mesentery and lungs of all of the animals showed extensive caseous tuberculosis.

These experiments indicate very strongly that neither the normal nor the allergic guinea pig infected with the human strain of tubercle bacilli is benefited by hyperpyrexia given for a period of time and at temperatures similar to those used in the treatment of man.

As we are attempting to treat pulmonary tuberculosis by means of hyperpyrexia it seemed desirable to ascertain if possible the temperature of the lung during such treatments. Accordingly peripheral lung temperatures were taken on three patients by inserting a thermocouple through the chest wall and into the lung to a depth of about 2 cm. The change in the room temperature from 61°F. to 72° and 80°F. caused only a slight change in the lung temperatures, the average of nine readings being 99.2°F. Humidity was also considered. The following tabulation shows the peripheral lung temperature under hyperpyrexia treatment.

METHOD USED TO HEAT LUNG	TEMPERATURE OF ROOM	RELATIVE HUMIDITY	MOUTH TEMPERATURE	RECTAL TEMPERATURE	TEMPERATURE OF LUNG
Diathermy	71°	66	101.6°	104.5°*	102.6°
Kettering Hypertherm	76°		102.3°	104.4°†	103.9°

* Rectal temperature was maintained for thirty minutes before temperature of lung was taken.

† Rectal temperature was maintained for twenty minutes before temperature of lung was taken.

This experiment indicates that in certain patients at least the peripheral lung temperature of human beings may be raised to 102.6°F. by general diathermy treatment and to 103.9°F. by the Simpson-Kettering Hypertherm. Insufficient data, however, are available at this time to draw any further conclusions.

From the experimental data cited above it appears impossible by present methods to raise the temperature of man to a degree and over a period of time sufficient to kill or even to attenuate tubercle bacilli. The human strain which is the most thermolabile apparently cannot be influenced by temperatures which can be tolerated by man. The experiments on guinea pigs were disappointing insofar as any beneficial effect of heat was concerned.

It appears possible, however, to raise the lung temperature to about

104°F. by general hyperpyrexia but it is doubtful if this temperature, which can be maintained only for relatively short periods of time, can have any inhibiting influence on the development of tubercle bacilli.

It is to be concluded then that whatever beneficial effects may be obtained from the use of hyperpyrexia in the treatment of tuberculosis must, except in rare instances, depend upon the resistance of the individual.

CLINICAL APPLICATION OF HYPERPYREXIA IN THE TREATMENT OF TUBERCULOSIS PATIENTS

Since September, 1932, hot baths, general diathermy, the Simpson-Kettering Hypertherm, hot moist air inhalations, the short-wave diathermy or the radiotherm have been employed as means of inducing artificial hyperpyrexia in the treatment of tuberculosis patients.

During this interval twenty-six patients were treated by baths or general diathermy or both. In the treatment of these patients, 263 short hot baths which raised temperatures to 102° to 103°F. by mouth with immediate cooling were used; 122 hot baths which raised temperatures to 104° or more by rectum and held it there for about an hour, and 369 general diathermy treatments in which the temperatures were maintained at 102° to 104°F. for four hours were given.

Of the patients treated, three had extrapulmonary tuberculosis and received 29 treatments of general diathermy, and twenty-three had pulmonary tuberculosis and received 725 treatments.

The three extrapulmonary cases were typed as to causative organisms. Two were found to be due to the human type of bacillus and one of these showed no change, the other was definitely improved as a result of treatment. The third case was found to be due to the bovine tubercle bacillus and he was made definitely worse by the treatment.

The pulmonary cases were far advanced, many with bilateral disease who had made little or no progress while in the Sanatorium, and even though they were on exercise, their ultimate outlook seemed hopeless. The results may be summarized according to X-ray findings as follows: two became worse, four showed no change, twelve showed slight improvement (a few showing a slight increase in disease with a slight improvement again under more treatment), and five cases showed moderate improvement.

The above report covered our first group of patients and seemed to indicate (1) that the far-advanced chronic case of pulmonary tuberculosis who is on exercise can tolerate this type of treatment without harm to

himself but without a great deal of improvement; (2) that the early cases might derive some real benefit from this type of treatment; (3) that if early cases were not available, then perhaps hyperpyrexia could be used on the advanced cases shortly after they were admitted and before their disease had become chronic.

That was our plan when we secured a Simpson-Kettering Hypertherm in October, 1934. In selecting patients for this type of treatment, we realized that bed-rest and collapse therapy were time-proved remedies of great value. Therefore, it would be impossible to determine the value of hyperpyrexia in the early cases should it be combined with them. Also, because hyperpyrexia was of undetermined value, we could not conscientiously substitute it for bed-rest or collapse therapy. Accordingly thirteen advanced cases with exudative disease but with only moderate cavitation, for whom bed-rest was considered to be inadequate and in whom collapse therapy was impossible, were selected for treatment with the Simpson-Kettering Hypertherm. The treatments were begun within two or three weeks after admission and in all 89 treatments were given. Originally it was planned to give one treatment a week for eight weeks at a temperature of 105° or more for four hours. However, it soon became apparent that bed-rest for only two or three weeks was long enough to weaken the heart muscle so that it could not stand the strain incident to hyperpyrexia treatment. Therefore, in only 24 per cent of these treatments were we able to attain a temperature of 104° or 105° and hold it for from one to three hours. In 42 per cent of the total treatments the temperature range was between 103.5° and 104.5° for one or two hours, and in 34 per cent the temperature range was 103.5° or less, frequently reaching only 102°F.

In two of the thirteen patients hyperpyrexia had to be discontinued after 5 treatments because they reacted poorly. Of the remaining eleven patients who had received 84 treatments, three showed no change on X-ray, six showed slight improvement and two moderate improvement.

Careful blood studies of the eleven patients were made by the same technician before and after treatment. The haemoglobin, the red cells and the white cells showed no important change. The percentage of the polymorphonuclears and of the monocytes decreased while the percentage of the lymphocytes increased. There was an improvement in the lymphocyte-monocyte ratio from 2.6 to 3.7. The eosinophils and basophils showed little change.

Because of the difficulties in obtaining satisfactory reactions with the Simpson-Kettering Hypertherm due to debility of the patients with the

result of a lack of marked improvement following treatment, the use of this machine was discontinued on April 12, 1935.

SUMMARY

From September, 1932 to April, 1935, thirty-four individuals with advanced pulmonary tuberculosis received 809 artificial hyperpyrexia treatments by means of baths, general diathermy and the Simpson-Kettering Hypertherm. According to X-ray, moderate improvement was noted in 21 per cent, slight improvement in 50 per cent, no change in 21 per cent, and 6 per cent of this group were definitely made worse. Even in the group who showed moderate improvement, cavities were not closed nor did the sputum become negative for tubercle bacilli. In some of those with slight improvement by X-ray, the change noted was so small as to be of theoretical interest only.

The laboratory studies made on this subject were disappointing in that (1) artificial hyperpyrexia for a period of time and at temperatures similar to those used in the treatment of man failed to prevent the development of tuberculosis in allergic and nonallergic guinea pigs infected with human tubercle bacilli.

(2) The growth of human tubercle bacilli *in vitro* was inhibited when heated continuously at 106°F. for three weeks. This did not destroy their virulence for guinea pigs.

(3) Heating human tubercle bacilli at 106°F. for five hours once or twice a week did not inhibit their growth.

(4) The five-hour "nongrowth point" and death point of human tubercle bacilli was found to be between 120° and 130°F.

It is possible to raise the temperature of the lung in man to 102.6° to 103.9°F. by means of general hyperpyrexia applied by either general diathermy or the Simpson-Kettering Hypertherm.

DISCUSSION

After three years of experience in the treatment of pulmonary tuberculosis by hyperpyrexia induced by means of baths, general diathermy or the Simpson-Kettering Hypertherm it is apparent:

(1) That the change in the chest as seen in the X-ray film occurs immediately or shortly after the completion of treatments. The only late effect that we can be sure of is the adverse effect of exhaustion produced by overtreatment. When this occurred the patient did not stand up well.

(2) That patients on exercise tolerate hyperpyrexia better than do bed patients. But every patient coming to Glen Lake Sanatorium starts as a

bed patient, and the patients on exercise consist of two groups, those who have more or less recovered from their disease and who therefore are not candidates for hyperpyrexia, and those whose ultimate prognosis may be poor, but who, in the opinion of their physician, have derived all the benefit they can from bed-rest and in whom collapse therapy is impossible. Most of the patients treated by baths and general diathermy were in that group. They tolerated the treatments better than the group of recently admitted patients who were still in bed and who were treated by the Simpson-Kettering Hypertherm. But neither group was benefited greatly by this type of treatment.

According to experimental studies the five-hour thermal nongrowth and death point of human tubercle bacilli is somewhere between 120° and 130°F. But man cannot tolerate such temperatures. This will explain why artificial hyperpyrexia in the form of baths, general diathermy or the Simpson-Kettering Hypertherm does not produce as good results in the treatment of tuberculosis as it does in the treatment of other diseases where the five-hour thermal death point is around 105° or 106°F.

It also suggests that to be of any definite value in the treatment of human beings, hyperpyrexia should result in a definite pulmonary heating over a fairly long period of each day without strain to the patient. In this manner the nongrowth effect of heat on the human tubercle bacillus may be used to its detriment and to the advantage of the host. Because of that the use of the Simpson-Kettering Hypertherm was discontinued early in the spring of 1935. Since then we have tried local methods of heating the lungs. These are without strain to the patients, they are well tolerated and can be given from four to six hours each day. The results of this type of treatment will be published later. To date they appear better than those obtained by hot baths, diathermy or the Simpson-Kettering Hypertherm. At least the strain of exhaustion is absent.

CONCLUSIONS

1. The thermal death point of the human tubercle bacillus has been found to be above temperatures tolerated by man.

2. Heating human tubercle bacilli *in vitro* for five hours once a week had no adverse effect upon their growth.

3. When this temperature was continuous for three weeks human tubercle bacilli failed to grow.

4. To be of any value in the treatment of tuberculosis, artificial hyperpyrexia should result in an increase in pulmonary temperature over a fairly long proportion of each day without strain to the patient.

We wish to thank Dr. G. Higgins, Mr. Herbert Grandlund and Miss Ada Washburn for their help in carrying out this study.

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MEDIASTINAL HERNIA FOLLOWING MASSIVE ATELECTASIS

Report of a Case in a Tuberculosis Patient

LEROY ELRICK

The commonest cause of mediastinal hernia is pneumothorax. The pressure of the air in the pleural cavity against a mobile mediastinum frequently causes its more elastic portions to bulge into the opposite half of the chest.

The case here reported is entirely different in its aetiology. A hernia of the left lung into the right hemithorax occurred as the result of massive atelectasis of the right lung. The shrinkage of the right lung, producing a strongly negative intrapleural pressure, was partly compensated for by herniation of the left lung through the upper anterior weak region of the mediastinum.

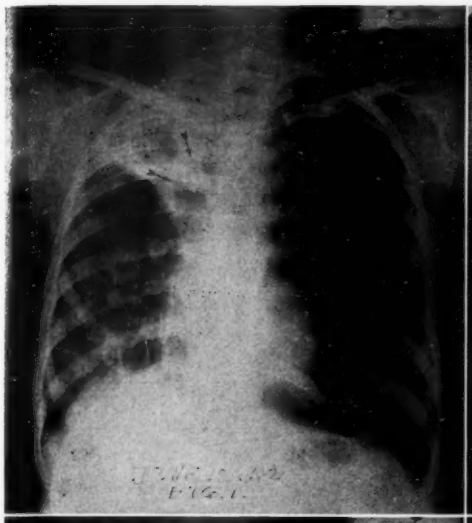
Case Report

The patient was seen at the Swedish National Sanatorium, Englewood, Colorado, and the case is reported by courtesy of the Medical Director, Dr. C. A. Bundsen.

A white woman of 27 was admitted to the Sanatorium on June 8, 1932 with a history of tuberculosis of three years' duration. Physical examination of the right lung showed diminished resonance and cavity signs at the apex, and coarse râles over the whole lung. In the left lung a few fine and medium râles were heard on cough over the upper lobe. A roentgenogram (figure 1) showed a cavity, 3 cm. in diameter, at the apex of the right lung, surrounded by dense fibrosis which had pulled the trachea over to the right. Areas of infiltration extended down to the base. There was a semilunar shadow, difficult of interpretation, concave toward the spine, extending from the anterior end of the first to the third rib. This shadow, which is rather indistinct in the reproduction of the X-ray film, is indicated by arrows, and will be referred to later. The left lung showed some small areas of infiltration and calcification. Numerous tubercle bacilli were present in the sputum. The haemoglobin was 85 per cent, the red cell count was 5,000,000, the leucocyte count was 7,000, and the sedimentation rate was 25 mm. in one hour, using a Cutler tube.

Pneumothorax had been attempted on the right side unsuccessfully in 1929. Right phrenicoexairesis was done July 12, 1932 by Dr. C. F. Hegner. This

Fig. 1



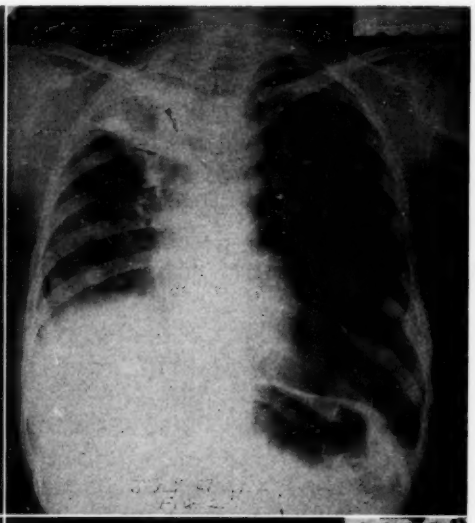
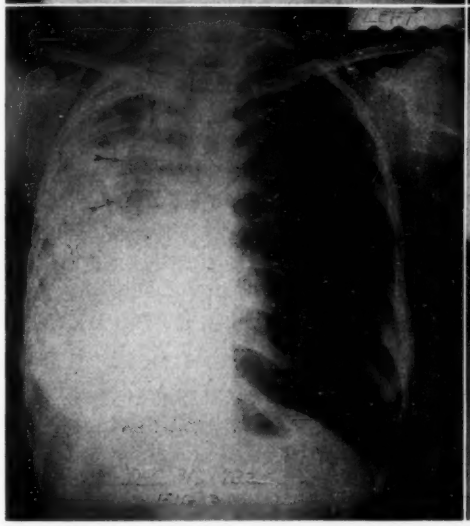


Fig. 2

Fig. 3



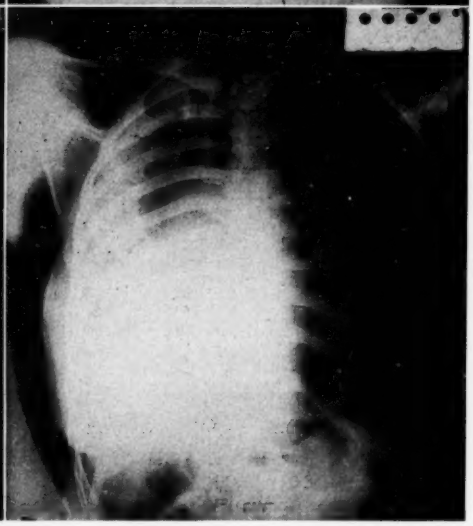


Fig. 4

Fig. 1. June 10, 1932. Soon after admission. The curved shadow in the upper right chest, indicated by arrows is referred to in the text.

Fig. 2. July 27, 1932. Showing rise of right diaphragm after phrenicectomy.

Fig. 3. December 31, 1932. Soon after the occurrence of massive atelectasis.

Fig. 4. May 22, 1933. Showing mediastinal hernia. The outline of the hernia of the left lung into the right hemithorax is indicated by arrows. The atelectasis is still present.

resulted in a marked rise of the diaphragm (figure 2). Following this the patient did well for several months. Her temperature was normal to 99°F. during this time, except for a rare elevation to 100°F. However, in December, 1932 (that is, five months after phrenicoexairesis) she had some chills, aching and a fever of 101°F. An X-ray taken December 31 showed evidence of atelectasis of the lower part of the right lung, with increased displacement of the trachea and heart toward the right. The size of the cavity at the apex was about the same. The semilunar shadow previously mentioned extended further to the right. (Figure 3.) Physical examination on January 16, 1933 supported the diagnosis of massive atelectasis of the middle and lower lobes of the right lung. Amphoric breathing and coarse râles were still heard at the apex. Pneumothorax was again attempted, but was unsuccessful on account of adhesions. The patient's condition did not permit thoracoplasty. Nevertheless she improved and during the next few months seemed better. The temperature subsided and then remained around normal to 99.2°F., and the daily amount of sputum decreased from three ounces in January to one ounce in April. The atelectasis persisted all this time. The patient complained of some pain and pulling sensation in the right chest and at times a feeling of distress behind the sternum on swallowing. There was marked dyspnoea on exertion.

In May there was a change for the worse. A septic temperature began, with occasional peaks as high as 103°F., sometimes accompanied by chills. The sputum, of a thick purulent character, increased to 3 ounces daily. An X-ray taken May 22, 1933 showed a marked difference from the preceding one. The atelectasis was still present; the cavity seemed a little smaller and less distinctly outlined, but the semilunar shadow previously mentioned extended far into the right chest, with a smooth edge, concave toward the spine, and situated between the anterior ends of the first and fourth ribs. The tissues enclosed within this shadow were more transparent to the X-rays than before (partly due to some difference in the technique of exposure of the film). The appearance of the semilunar shadow was somewhat suggestive of a large cavity, but the lateral wall was unusually smooth and regular, and a medial wall could not be made out. (Figure 4.)

A remarkable alteration in the physical signs was now observed to have taken place. The amphoric breathing and coarse râles heretofore present at the right apex anteriorly had disappeared, to be replaced by vesicular breathing without râles. Also, the previously impaired percussion note over this area gave place to normal resonance. Amphoric breathing and coarse râles remained as before over the upper part of the lung posteriorly. The interpretation of the change in physical signs and X-ray was difficult until Dr. W. N. Beggs, in consultation, suggested that the condition was one of hernia of the left lung through the upper anterior "weak spot" of the mediastinum. This

would account for the physical signs of normal lung tissue to the right of the sternum and for the curved shadow in the X-ray film. Autopsy later proved this to be the correct explanation. The patient's toxic symptoms continued, she became gradually weaker, and died on June 27.

At autopsy there was found a massive atelectasis of the right lung, caused by the pressure of an enlarged calcified lymph node upon a bronchus. Unfortunately, notes made at the time do not state exactly how much of the lung was involved in the collapse, and after an interval of three years it is impossible to remember this point, but it is certain that the atelectasis was extensive and the X-ray film would indicate that the lower and middle lobes were airless. Multiple cavities remained open at the apex of the right lung. The right dome of the diaphragm was at the level of the fourth interspace. Most of the right pleural cavity was obliterated by firm adhesions. Tubercles varying in size from that of a pinhead to a walnut were scattered throughout the lung. There was a tongue-like projection of the left lung behind the sternum and anterior chest-wall and in front of the right lung, which it compressed to some degree anteroposteriorly. This hernia of the left lung extended past the *right* midclavicular line, pushing the mediastinal pleura ahead of it. The right border of the herniated left lung corresponded exactly with the position of the semilunar shadow seen on the X-ray film (indicated by arrows in figure 4). The tracheobronchial lymph nodes were greatly enlarged on both sides. The left lung contained many small hard tubercles. The cause of death was chronic pulmonary tuberculosis. It was not thought that the mediastinal hernia had any particular influence on the course of the disease.

COMMENT

The sequence of events had apparently been as follows: an enlarged tuberculous lymph node compressed the right main bronchus, resulting in a massive atelectatic collapse. The decreased size of the lung was compensated for in the way usual to such cases, by elevation of the diaphragm and displacement of the heart toward the affected side, and in an additional way which is less common, namely, herniation of a part of the opposite lung into the involved hemithorax.

The case is reported because a large mediastinal hernia due to this cause is unusual, and because opportunity to confirm the diagnosis was given at autopsy. The peculiar X-ray appearance of the hernia gave rise to various opinions as to its interpretation, until the question was finally settled at the postmortem examination. Whether the smaller semilunar shadows indicated by arrows in the first three figures represent the hernia in an earlier stage of its development is not known.

In a review of the literature in the English language only one case of a large mediastinal hernia with the same aetiology was discovered. Korol (1) reported an instance, in which the hernia was almost exactly the same size as the one under discussion, but occurred in the left side of the chest, following atelectasis of the left lung. In his case also the massive collapse was caused by obstruction of a bronchus by the pressure of a tuberculous lymph node.

Why did the hernia occur in the upper anterior part of the chest? Because here is situated the weakest part of the mediastinum. Nitsch (2) described two "weak places" in the mediastinum. The first is above and in front of the pericardium and behind the upper end of the sternum. The second is in the lower posterior part of the thorax, behind the heart. Bulging takes place more easily in the first location, that is, the anterior-superior part of the mediastinum.

Cases have been reported of a beneficial effect of atelectasis in tuberculosis (3), but in the instance which is the subject of this paper the improvement was only temporary.

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REINDUCTION OF PNEUMOTHORAX

ARNOLD SHAMASKIN AND JACOB ROGOFF[1]

Linked to the question of reinduction of pneumothorax is the most perplexing problem in the entire subject of pneumothorax, namely, its duration.

The management of pneumothorax is greatly influenced by the almost universal belief that interruption of this treatment is invariably followed by obliteration of the pleural space, making reinduction impossible. This fear of permanently losing the pleural space dominates our minds whenever the question of terminating pneumothorax comes up and is the deciding factor against it in the vast majority of cases. The problem, however, would be much simpler if reinduction of pneumothorax were possible in the majority of cases.

Thus Burnand (1) reasoned that it would be useless to prolong pneumothorax indefinitely if we were sure that the first pneumothorax, having resulted in a cure of the pulmonary lesion and abandoned, could be reestablished when necessary. As soon as we are fairly certain that the lesions are healed we would interrupt the treatment to resume it when indications arise. If, however, the two pleural surfaces become adherent after reëxpansion of the lung, pneumothorax could not be abandoned so easily.

After reviewing fourteen cases of attempted recollapse, Burnand comes to the conclusion that the occurrence of fluid in the pleural space, no matter how small in amount or how transitory, is responsible for pleural symphysis when the lung is allowed to reëxpand. According to Burnand, pleural effusions occur in 50 to 80 per cent of pneumothorax patients. The trauma caused to the pleura in the process of inflation, or even the mere presence of a gas in the pleural space, is, in the opinion of Burnand, sufficient to cause adhesions between the pleural layers after cessation of pneumothorax in any case which has been maintained for some months. He, therefore, concludes that we must expect, with rare exceptions, obliteration of the pleural space in all cases within a short time after pneumothorax has been abandoned.

[1] Montefiore Hospital Country Sanatorium, Bedford Hills, New York.

Cases in which pneumothorax was successfully reëstablished have been viewed more or less as medical curiosities. The American literature is singularly meagre in this respect.

Rubin (2) reports a patient, who had pneumothorax for a period of two years. An effusion was present during the course of this pneumothorax. Four years later pneumothorax was reëstablished in spite of a greatly thickened pleura seen on X-ray and confirmed by autopsy.

Geer (3) reëstablished a pneumothorax three months after it had been abandoned.

We find, however, more frequent reference to the subject of reinduction of pneumothorax in the foreign literature.

Thus Eizaguirre (4) reported in 1921 a patient who had a pneumothorax on the right side for a year and a half. When a new lesion appeared in the left lung the right was reëxpanded by aspiration and the left was collapsed. Six to eight months afterwards recrudescence having taken place in the right lung it was successfully recollapsed. Hutchinson (5) reëstablished pneumothorax more than six years after the last refill of the first pneumothorax, while Pearson (6) successfully reëstablished pneumothorax in two patients: in one it was given for eight and a half years and reëstablished two years after the last refill; in the other one the lung was recollapsed after an interval of fifteen months. In a case reported by Hirshberg pneumothorax was given for three months and then reëstablished after an interval of ten months.

Zambianchi (7) calls attention to the fact that of the many patients treated with pneumothorax very few come back with indications for reinduction. Of 280 cases treated by him with artificial pneumothorax between the years 1924 and 1930, only seven came back to him with indications for reinduction of pneumothorax, and one to continue a reëstablished pneumothorax. Of these eight cases, four had excellent pneumothorax the second time, two had fairly effective pneumothorax, while in two reinduction was impossible. In one of the cases pneumothorax was reëstablished after a lapse of three and a half years, in one two years and in one seventeen months after the first pneumothorax; in all the other cases the attempt to reëstablish pneumothorax was made less than a year after the first pneumothorax was abandoned.

According to this author adhesions are formed by spread of the inflammatory process from the lungs to the pleura and therefore adhesions are more apt to form if pneumothorax is discontinued before there is a complete clinical recovery or when pneumothorax is not reinduced as

soon as symptoms of reactivation of the tuberculous process appear. While this probably does happen occasionally, it could not be a very potent factor in the formation of adhesions, otherwise pneumothorax in general, and so called selective collapse in particular, would have been impossible in the vast majority of cases since every tuberculous process has at one time or another been active.

This author also warns against continuing pneumothorax beyond clinical recovery because too long a treatment also predisposes to adhesions on account of the greater liability to pleural complications and on account of the change produced in the pleural surfaces by prolonged pneumothorax.

He reasons, therefore, that if pneumothorax is discontinued only after complete recovery has taken place and if reinduction is attempted at the first sign of reactivation of the lesion, and also if a pleurisy of long duration has not existed before, pneumothorax can be reëstablished.

De la Torre (8) reëstablished pneumothorax in two patients: in one pneumothorax was maintained for three and a half years and then reestablished eight months after the last refill, the lung having fully reexpanded; in the other patient, pneumothorax was reëstablished after the lung had been fully reëxpanded for two years. He concludes that reinduction of pneumothorax is possible even if fluid was present during the first pneumothorax, that when pneumothorax is reëstablished it takes the same form as the first pneumothorax, that duration of pneumothorax treatment should depend on the type and age of the lesions, and that, during reëxpansion and some time after, rest should be maintained.

Mantoux (9) relates the case of a patient who was under pneumothorax treatment for nine years. It was then voluntarily discontinued. Six years later reactivation of the disease took place. In spite of marked retraction of the chest, displacement of the trachea and marked reduction in the pulmonary field, pneumothorax was attempted. On entering the chest the pleura was found thick and hard but the pleural space was not obliterated. Although intrapleural pressure was strongly positive and after the second inflation only 50 to 100 cc. of air could be given, pneumothorax was reëstablished and was followed by marked improvement in the patient's condition and disappearance of symptoms.

Pneumothorax was reëstablished by Longo (10) in two patients: in one sixteen months and in the other four months after the last inflation. He believes that reëstablishment of pneumothorax is possible in most

cases which have not been complicated with pleurisy and that it should be discontinuned when the lesion is healed. He admits, however, that there are many diverse opinions as to what constitute the signs of recovery particularly when the lung is collapsed. He also thinks that recent lesions require shorter periods of treatment than older lesions, and quotes Constantini and also Baer, who advise as short a period of pneumothorax treatment as a few months for recent exudative lesions, which have a tendency to heal by resolution (*restitutio ad integrum*) even when cavities are present.

Bluhm (11) reports three patients in whom pneumothorax was reestablished. In one case pneumothorax was administered on the right side for three years and then discontinued on account of spread to left lung, which was then collapsed. Pneumothorax was kept up on the left side for five years. Three years later, or eight years after the pneumothorax on the right side was interrupted, it was reëstablished on account of reappearance of symptoms. Pneumonolysis was resorted to in this patient in order to bring about a satisfactory collapse. In the second patient pneumothorax was administered on the left side for six months and discontinued on account of persistent fever and pneumothorax was induced on the right. One year and nine months after pneumothorax on the left side was interrupted it was reëstablished. However, after three intrapleural pneumonolyses, a cavity was still open. In the third case pneumothorax was maintained for seven years, abandoned, and reëstablished after an interval of three and a half years.

Kirch (12) induced pneumothorax in two patients following febrile exudative pleurisy confirmed by tap, while Frisch and Vita (13) cite Ameuille who reports a complete pneumothorax after febrile exudative pleurisy with effusion.

Our successful reinduction of pneumothorax after an interval of nineteen months in a patient who previously had received pneumothorax for a period of two years influenced us to undertake the study of this problem on a larger scale.

We began to select, for interruption of pneumothorax, patients who for at least six months were symptomless with negative sputum on concentration, whose temperature, pulse and sedimentation rate were normal and who either maintained or continued to gain weight on exercise. In other words, these patients could have been classed as arrested in the absence of pneumothorax. The patients selected for this experiment were all young adults with more or less recent exudative lesions and thin-

walled cavities, the type of lesion in which recovery frequently takes place by resolution in a comparatively short time. This group includes five patients.

The collapsed lung was permitted to reëxpand under careful supervision. If it appeared reasonably clear of disease on almost total reexpansion it was allowed to come out completely; otherwise it was immediately recollapsed.

After varying intervals of time the presence or absence of a free pleural space was determined by a single experimental inflation in those who remained well. In the other cases recollapse was necessary on account of reactivation of the lesion. Experience shows that we can be reasonably certain of the presence of a free pleural space if marked negative manometric readings with wide fluctuations are obtained on the first needle puncture of the chest and if, after the introduction of several hundred cubic centimetres of air, the intrapleural pressure becomes less negative or only slightly positive, if fluctuations remain fairly wide and the patient experiences no serious discomfort.

Through a coincidence there were admitted to our Sanatorium at the time this study was carried out four patients with indications for reinduction of pneumothorax discontinued elsewhere, and one patient in whom pneumothorax was discontinued at our Sanatorium four years previously. Altogether we had eleven opportunities in ten patients (one a bilateral pneumothorax) to determine whether or not their pleural cavities were free from adhesions after pneumothorax had been discontinued.

Of the five patients, whose pneumothorax was discontinued at our Sanatorium, two were discharged as arrested. These have remained well, are now working, and are in no need of further treatment. They received pneumothorax for twenty-two and sixteen months respectively. The third patient of this group, who received pneumothorax for twenty-nine months on the right side before it was voluntarily discontinued, was discharged as a quiescent case with a pneumothorax on the opposite side. He is living a partially restricted life at home and is still receiving pneumothorax on the left, while the right lung has remained clear. Before the discharge of these three patients from the Sanatorium, we introduced a needle attached to a manometer into the pleural cavity of each and found that two of them had obliterated six and twelve months respectively after discontinuation, while the third still had a free pleural space eight months after pneumothorax was abandoned. The remaining two patients of this group, including the bilateral case, developed posi-

tive sputa, increased sedimentation rates and other signs of activity. Pneumothorax was successfully reinduced in both and they are still under this treatment. *As far as we are aware the bilateral case, referred to above, is the only one reported in which both lungs were successfully re-collapsed after complete reëxpansion had taken place.*

Of the remaining five patients of our series, two were abandoned before coming to this Sanatorium for reasons which we were unable to determine. These had received pneumothorax for periods of only two and four months, respectively. In two other patients of this group pneumothorax was induced at our institution and continued, one for nine months, and one for twenty-four months. The latter two patients had been working and were readmitted with relapses two and three years respectively after discharge. The four patients just enumerated were considered suitable for pneumothorax therapy again, and we found that we could readily reinduce and successfully maintain an effective pneumothorax in all four. The last patient of our series came to us as a case of alternating pneumothorax. She had received pneumothorax on the left side for a period of ten months before admission to our Sanatorium. The pneumothorax had been abandoned on this side because of progression in the right lung, which had been collapsed effectively, so that on admission we found her with an effective pneumothorax on the right side. After fifteen months at our Sanatorium we were forced to discontinue the pneumothorax on the right side because of recrudescence of the lesion in the left lung. We were able to recollapse this lung and maintained the pneumothorax for one year before spontaneous obliteration took place.

CASE REPORTS

1: M. D., male, age 23. First admission October 14, 1931 with a history of onset July, 1931. Examination on admission revealed scattered areas of mottling in both midlung fields with a cavity one inch in diameter in the left second interspace anteriorly. Sputum was negative throughout his first stay at the Sanatorium. Sedimentation index was 8. Marked improvement took place in this case on routine sanatorium care and the cavity in the left lung disappeared by April 12, 1932. In September and October, 1932, there were brief elevations of temperature to 100°F. and a roentgenogram taken in November, 1932 showed increased mottling in the right lung. This cleared up by January, 1933 when he left the institution of his own accord.

The patient returned to us on June 9, 1933 with a history of increased cough and expectoration since discharge. Sputum was now found positive for the

Fig. 1A. June 13, 1933 Fig. 1B. February 1, 1934 Fig. 1C. March 22, 1934 Fig. 1D. October 31, 1935

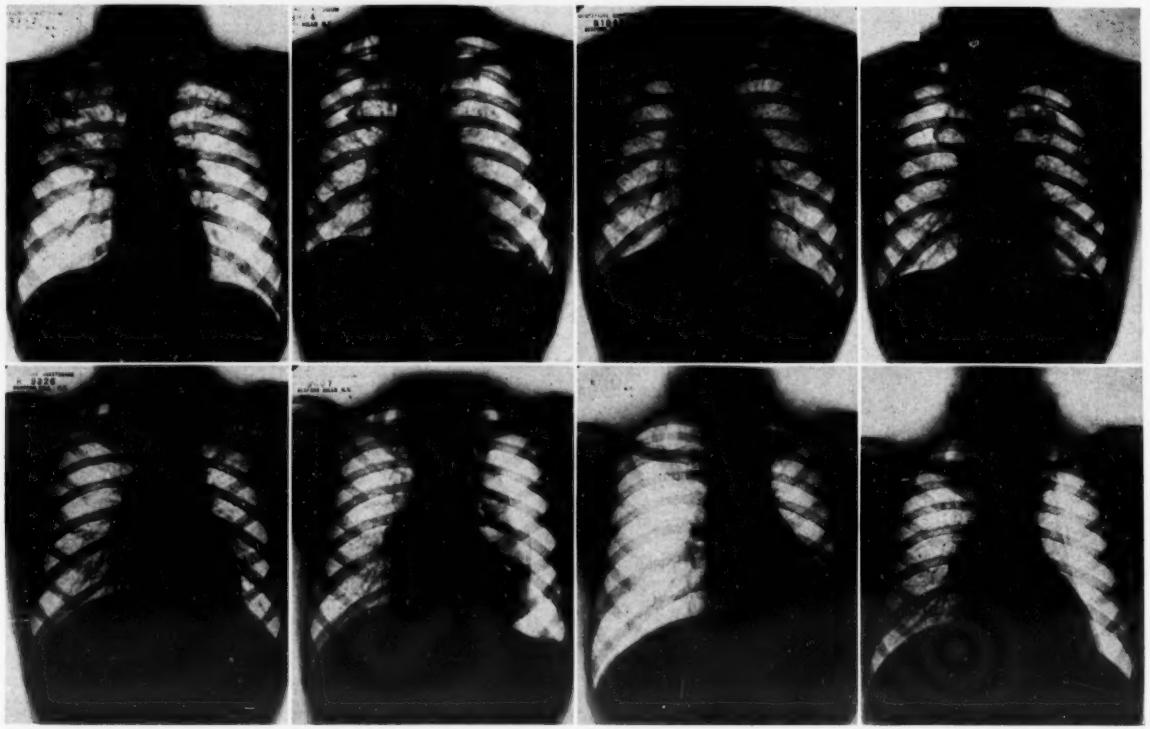

Fig. 2A. May 6, 1933 Fig. 2B. October 5, 1933 Fig. 2C. March 14, 1935 Fig. 2D. October 31, 1935

PLATE 1

first time. Examination revealed an exudative lesion involving the upper half of the right lung and upper one-third of the left with a cavity two inches in diameter in the right infraclavicular region and a cavity one-half inch in diameter in the left first interspace anteriorly (figure 1A). Sedimentation index was 22. Pneumothorax was induced on the right side July 27, 1933, 500 cc. of air having been introduced with an intrapleural pressure of −3 −9 before and −5−3 at the end of inflation. A roentgenogram taken October 20, 1933 showed an effective pneumothorax on the right side with marked progression on the left side. Although the sputum was negative and sedimentation index remained low, pneumothorax was induced on the left side October 30, 1933 and a bilateral pneumothorax was maintained for nine months (figure 1B). Because of the absence of all constitutional symptoms, negative sputum and normal sedimentation rate since the induction of pneumothorax on the left side, the latter was allowed to reëxpand after nine months and the right lung after fifteen months of collapse. Small amounts of fluid were visible in each costophrenic sulcus on and off during the course of treatment but no exudative pleurisy was ever present. A roentgenogram taken November 22, 1934 (figure 1C) showed scattered areas of dense mottling and fibrosis above the level of the second right interspace anteriorly and numerous areas of beginning calcification above the level of the fourth left rib anteriorly. In comparison with a film taken previously the pneumothorax has completely disappeared from both sides and there was marked evidence of healing throughout. After discontinuation of the bilateral pneumothorax the patient remained symptomless and maintained his weight, his sputum remained negative, and the sedimentation index was normal. On April 11, 1935, ten months after pneumothorax was discontinued on the left side, we experimentally introduced a needle connected with a manometer into this pleural space and 200 cc. of air were injected with a manometric reading of −4−5 before and −6−2 at the end of the inflation, thus proving that obliteration had not taken place in the left pleural space. Toward the end of April, 1935, the patient's sputum became positive, coincident with the return of symptoms, loss of weight and evidences of progression by X-ray. Pneumothorax was then successfully reinduced on the right side May 2, 1935, seven months after discontinuation, 600 cc. of air having been given with manometric readings of −14−5 before and −6−2 at the end of inflation. He received weekly refills of 500 cc. with negative pressure. Patient's sputum soon became negative again. By September, 1935 progression with cavity formation was noted in the left lung and pneumothorax was thereupon successfully reëstablished on this side, 14 months after discontinuation, 600 cc. of air having been given with pressures of −10−5 before and −7−4 at the end of inflation. Thus bilateral pneumothorax was reëstablished seven and fourteen months respectively after the first pneumothorax was abandoned (figure 1D). At present he is still a patient

at this Sanatorium. He received bilateral pneumothorax up to the middle of October, 1936 when a massive effusion developed on the right side and pneumothorax on this side had to be abandoned. Sputum is now negative for tubercle bacilli.

2: C. E., male, age 29, admitted January 16, 1933 with a history dating back to October, 1932. Examination on admission revealed a lesion involving the upper third of the left lung with a cavity one-half inch in diameter. Sputum was positive for tubercle bacilli and sedimentation index was 26. He did well on bed-rest, gaining nine pounds, until May, 1933 (figure 2A). Because of a persistently positive sputum and roentgenological evidence of slight progression, pneumothorax was successfully induced on the left side May 22, 1933. A trace of fluid was noted in the left costophrenic sulcus August, 1933, which persisted until November, 1933 (figure 2B). He received his last refill on October 18, 1934. Four hundred cc. of air were then administered with pressures of −13−4 before and −9−2 at the end of inflation. At the time of discontinuation a trace of fluid was again visible in the left pleural cavity. Pneumothorax was discontinued in this case after 17 months of treatment because patient had been symptomless with a negative sputum for the last nine months. Sedimentation index came down to 11. A roentgenogram taken November 22, 1934, one month after the last refill, showed a reëxpanding left lung with no evidence of disease. A roentgenogram taken January 10, 1935 showed a minimal lesion with a few areas of mottling in the left apex and a thickened pleura particularly at the base. Five months after pneumothorax was abandoned a routine sputum examination revealed tubercle bacilli on concentration, but a roentgenogram taken at this time revealed no new foci (figure 2C). Because of a persistently positive sputum it was thought best to attempt recollapse of the left lung. This was successfully carried out on October 10, 1935 when 500 cc. were introduced into the left pleural space with pressures of −15−12 before and −7−4 after induction, in spite of a roentgenological appearance indicating a greatly thickened pleura (figure 2D). The first five refills, averaging 600 cc., were spaced at semiweekly intervals. The manometric readings remained negative both before and at the end of refills. Sputum became negative January, 1936 and has remained negative since. The patient was discharged, still receiving pneumothorax, on January 19, 1936 and was accepted for rehabilitation at the Altro Work Shops, where he was still employed in December, 1936. His pneumothorax is being continued at an out-patient clinic. His sputum is negative for tubercle bacilli.

3: A. R., female, age 24, admitted November 21, 1932 with a history of onset in 1931 following a pregnancy. Pneumothorax was instituted on the left side in September, 1931, followed by disappearance of all symptoms of activity.

She felt well until May, 1932, at which time she began to lose weight and her symptoms returned. A roentgenogram taken at this time revealed new involvement in the right lung. Pneumothorax was discontinued on the left side and induced on the right in June, 1932. A roentgenogram taken on admission to our Sanatorium November, 1932 showed a 65 per cent effective pneumothorax on the right with a trace of fluid in the costophrenic sulcus. A large area of infiltration was visible at the level of the second right interspace anteriorly. Sputum remained persistently negative on concentration and sedimentation index remained normal. Pneumothorax was continued on the right side with weekly inflations of 400 cc. always with negative final readings. In January, 1933 she began running a slightly elevated temperature in the evening and the sedimentation index rose from 9 to 20. A roentgenogram taken February 6, 1933 showed new involvement in the middle third of the left lung. Bed-rest was followed by disappearance of symptoms. However, in July of the same year the symptoms returned and an X-ray film showed new cavitation in the left midzone. By September, 1933 there was considerable increase in the mottling on the left side and her sedimentation index rose to 24 but the sputum remained negative. Pneumothorax was discontinued on the right side and in September, 1933, 15 months after interruption of pneumothorax treatment on the left side, the lung was recollapsed. She received 400 cc. on reinduction with readings of −13−8 before and −2+4 at the end of inflation. The patient received refills twice weekly for the first two weeks and then once weekly thereafter, averaging 400 cc. per refill with slightly positive final manometric readings. She continued to receive pneumothorax until September, 1934 when an obliterative pleuritis set in and pneumothorax had to be abandoned. She was discharged August 9, 1936 at her own request, with her disease progressive.

4: A. C., female, age 17. First admitted May 5, 1930. She dates the onset of her illness back to November, 1929. Examination on admission revealed an exudative tuberculosis involving the middle third of the right lung and the entire left lung, with a cavity about one inch in diameter in the midzone of the latter. Her sputum was positive. She had a low-grade temperature, cough and expectoration. Pneumothorax was induced on the left side on June 19, 1930. She received weekly refills all through her stay in the Sanatorium and was discharged on June 21, 1931. Upon discharge her sputum was negative. No evidence of fluid was apparent at any time during the pneumothorax treatment. She continued to receive pneumothorax at an out-patient clinic until June 17, 1932, when it was voluntarily discontinued, two years after induction. There is no record of fluid having been seen in the left pleural space. In July, 1932 she spent a month at this Sanatorium as a vacationist from the Altro Work Shops. A roentgenogram taken at that time showed

marked fibrosis in the lower two-thirds of the left lung with a thickened pleura at the base. Her sputum remained negative and her sedimentation index was 7. In June, 1933 she was readmitted as a patient on account of increased cough, expectoration, night sweats, loss of weight and slight haemoptyses. A roentgenogram taken at this time showed an exudative tuberculosis involving the upper third of the right lung and the upper half of the left with cavitation in each infraclavicular region. Sputum was positive and sedimentation index was 19. After six months of routine sanatorium care a roentgenogram revealed retrogression in the right lung with disappearance of the infraclavicular cavity and progression in the left. Sputum still remained positive. Pneumothorax was successfully reinduced on the left side January, 1934, 500 cc. being given with intrapleural pressures of −18−14 before and −7−3 at the end of inflation. For the first three weeks she was given refills twice weekly averaging 400 cc. at a refill with slightly positive final pressures, and then weekly amounts of from 300 cc. to 400 cc. She was discharged from the Sanatorium October 21, 1934 with negative sputum and a sedimentation index of 12. According to a follow-up report received July, 1936 she is in excellent condition, is married, works 6 hours a day at the Altro Shops, does not expectorate and receives pneumothorax refills once every three weeks.

5: M. P., male, age 18, admitted May 13, 1935 with a history dating 18 months before admission. According to patient's statement pneumothorax was induced on the right side in February, 1934 and was abandoned three months later in June, 1934, when he was told he was well enough to return to school. He returned to school in December, 1934 where he did a few months work and participated in athletics. A roentgenogram taken three weeks before admission to this Sanatorium revealed persistent tuberculosis in the right lung. A sputum examination at this time was positive for tubercle bacilli. On admission to our Sanatorium sputum was positive for tubercle bacilli, sedimentation index was 11 and a roentgenogram revealed an exudative lesion involving the upper half of the right lung with a cavity an inch in diameter in the infraclavicular region. These findings together with the fact that our X-ray film showed marked progression, as compared with the one taken a year ago, were definite indications for collapse therapy without delay. There was no history of a pleural effusion in this case. Pneumothorax was successfully reinduced on the right side May 30, 1935, 11 months after the last inflation. Six hundred cc. were given with intrapleural pressures of −8−4 before and −6−2 at the end of inflation. This patient received inflations of 500 cc. twice weekly for the first three weeks and then 400 to 600 cc. once a week either with negative or slightly positive final pressures until December 22, 1935, when he left the institution of his own accord with a positive sputum and abandoned his pneumothorax.

6: E. L., male, age 28, admitted June 3, 1935. Onset while in Germany, March, 1934. A roentgenogram taken in April, 1934 revealed pulmonary tuberculosis involving the left lung, and pneumothorax was instituted on this side May 11, 1934. He received only eight inflations of 400 cc. each at weekly intervals after which pneumothorax was discontinued for reasons unknown to the patient. He gave no history of an effusion complicating his first pneumothorax but a trace of fluid is visible on a roentgenogram received from Germany. He came to the United States in August, 1934. He remained well until two months before admission when he again developed a slight productive cough and began to tire easily. He was seen by a physician who advised sanatorium care. A roentgenogram taken on admission to this Sanatorium, June, 1935, revealed an exudative tuberculosis involving the entire left lung with marked cavitation in the infraclavicular region and a lesion in the middle third of the right. Sputum was positive for tubercle bacilli and sedimentation index was 21. Pneumothorax was successfully reëstablished June 10, 1935, 12 months after it was abandoned, 500 cc. being given with intrapleural pressures of −13−9 before and −8−9 at the end of inflation. Following the reinduction he was given weekly refills of 500 cc. and an effective collapse of the left lung was obtained. Sputum became negative two months later and sedimentation rate returned to normal. He remained symptomless throughout the rest of his stay in the Sanatorium and was discharged June 21, 1936. He is now employed at the Altro Work Shops and is receiving pneumothorax at an out-patient clinic. Sputum is negative for tubercle bacilli.

7: J. B., male, age 31, first admitted September 8, 1930. Onset in 1929 with cough and loss of weight. Examination on admission revealed an exudative tuberculosis, involving the upper two-thirds of the right lung and the upper one-third of the left with considerable cavitation in both. Sputum was positive for tubercle bacilli. In November, 1930, pneumothorax was induced on the right side, 300 cc. being given with manometric readings of −1−3 before and −1−2 at the end of inflation. He received 400 cc. at weekly intervals always with negative final readings. Pneumothorax was discontinued on July 2, 1931 because the pleural space could not be found on several attempts. No fluid was seen in the right pleural space at any time. He was discharged August 7, 1932 as apparently arrested. Following his discharge from this Sanatorium he worked in the Altro Shops until April, 1934 when he was classed as a rehabilitated case. He was readmitted to this Sanatorium on August 19, 1935 with a history of eight months' cough and a positive sputum. Examination on readmission revealed far advanced pulmonary tuberculosis, predominantly exudative in character, involving the upper half of the right lung with cavitation. Sputum was positive for tubercle bacilli and sedimentation index

was 23. Pneumothorax was successfully reinduced on the right side on August 26, 1935, four years and a month after the last refill, 500 cc. being given with intrapleural pressures of −5−2 before and −4+2 at the end of inflation. He received weekly reinflations subsequently and a satisfactory collapse of the right lung was reëstablished. His sputum became negative and sedimentation rate returned to normal. He was discharged from the Sanatorium on April 26, 1936. At the present time he is still under pneumothorax treatment at an out-patient clinic. Sputum is negative.

8: B. S., male, age 26, admitted February 10, 1931 with a history dating back six years during which time he was a patient at four other institutions where he received routine sanatorium care. Examination on admission to our institution revealed an exudative tuberculosis involving the upper halves of both lungs with a cavity one inch in diameter in the right infraclavicular region. Sputum was positive for tubercle bacilli and sedimentation index was 12. Pneumothorax was instituted on the right side May, 1932. He remained under pneumothorax treatment until March, 1934, a period of 22 months, receiving weekly refills of about 500 cc. usually with negative final pressures. Traces of fluid were visible on several occasions during the treatment. Sputum turned negative in July, 1933 and remained so until the time of his discharge on April 15, 1935. On November 1, 1934, eight months after pneumothorax was voluntarily discontinued, we experimentally introduced a needle into the right pleural cavity to determine whether or not the pleural space was free. We found that we were able to introduce 400 cc. of air with intrapleural pressure of −11−6 before and −3+1 at the end of inflation. He has been rehabilitated from the Altro Shops and is considered arrested.

9: L. F., male, age 28, admitted December 1, 1932. Onset with cough and haemoptysis. Examination on admission revealed an exudative tuberculosis, involving the entire left lung with a cavity about a half inch in diameter in the infraclavicular region. Sputum was positive for tubercle bacilli and sedimentation rate was 10. Pneumothorax was induced on the left side June, 1932 and continued 16 months until October, 1934, when it was voluntarily terminated because patient was symptomless. Sputum was negative during 10 months and sedimentation rate was normal. Traces of fluid were seen on and off during pneumothorax treatment. Six months after discontinuation of pneumothorax an attempt was made to see if the left pleural cavity was free from adhesions by inserting into the left pleural space a needle connected with a manometer. The initial reading was −16−10 but after a small amount of air was given the patient complained of pain in the chest and a high positive pressure characteristic of pocketing was observed. Discontinuation of pneumothorax in this patient has resulted in obliteration of the pleural space.

Since discharge this patient has been working in the Altro Shops 7 hours a day and is in excellent condition. Sputum is negative and he is considered arrested.

10: S. S., male, age 20, admitted May 16, 1932. Onset in April, 1931 with a persistent nonproductive cough. In May, 1931 he had a haemoptysis of 4 ounces. He was admitted to a hospital where pneumothorax was induced on the right side. A roentgenogram taken on admission to our Sanatorium showed a fairly extensive pneumothorax on the right side and scattered areas of infiltration in the left middle third. Sputum was negative for tubercle bacilli and the sedimentation index was 15. He was given weekly refills of 400 to 500 cc. of air, always with final negative readings. An X-ray taken March 9, 1933 showed the pneumothorax on the right side to be more extensive and a picture taken August, 1933 showed considerable absorption of the infiltrations on the left side. The sputum remained negative until November, 1933 when it became positive and the sedimentation index rose from 13 to 21. A roentgenogram taken at this time showed progression in the left infraclavicular region with a small cavity. Pneumothorax was then instituted on the left side. Shortly after that the pneumothorax on the right had to be abandoned on account of dyspnoea. Sputum soon became negative. During the reëxpansion of the right lung a moderate effusion appeared in the right pleural space. By February, 1934 the right lung had entirely reëxpanded. On November 22, 1934 we experimentally introduced a needle into the right chest and found the pleural space obliterated. This patient was discharged as quiescent in August, 1935 and advised to continue pneumothorax on the left side. He was readmitted to our Sanatorium on January 25, 1937 with an effective pneumothorax on the left side and progression in the apex of the right lung about three years after pneumothorax on that side had been discontinued.

DISCUSSION

Our own experience with reinduction of pneumothorax as well as our review of the literature on the subject bring out some interesting and practical points.

It would seem that the mere presence of air in the pleural space or small transitory effusions do not, as a rule, cause obliteration of the pleural space when pneumothorax is terminated, and the general belief that pleural symphysis takes place almost invariably within a short time following the cessation of pneumothorax is not substantiated in the light of our experience.

We are inclined to believe that this impression is created because the majority of pneumothoraces are not discontinued voluntarily but are

continued indefinitely until they terminate themselves, either by an obliterative pleuritis, an exudative pleurisy or a massive effusion, which make reinduction impossible; or by some other complication, which contraindicates pneumothorax permanently. If, however, the patients, in whom pneumothorax was voluntarily discontinued, be selected from all the patients who received pneumothorax, as was done by us, the percentage of successful reinductions would be found quite high.

The longest duration of the first pneumothorax among our cases which were successfully reinduced was two years (see table 1). It is possible

TABLE 1*

	DURATION OF ILLNESS	DURATION OF FIRST PNEUMOTHORAX	INTRAPLEURAL FLUID	INTERVAL BETWEEN FIRST AND SECOND PNEUMOTHORAX	WAS REINDUCTION SUCCESSFUL	DURATION OF SECOND PNEUMOTHORAX TO JANUARY, 1937
	years	*months*		*months*		*months*
1: M. D.						
Right	5	15	Trace	7	Yes	18
Left	5	9	Trace	14	Yes	14
2: C. E.	6	17	Trace	12	Yes	11
3: A. R.	5	10	No	15	Yes	12
4: A. C.	6	24	No	19	Yes	13
5: M. P.	2½	4	No	11	Yes	35
6: E. L.	2	12	Trace	12	Yes	17
7: J. B.	7	9	No	4	Yes	15
8: B. S.	10	22	Trace	8	Yes	
9: L. F.	4	16	Trace	6	No	
10: S. S.	5	29	Moderate	12	No	

* No massive effusion or exudative pleurisy occurred in any of the cases reported here before reinduction was attempted.

that with pneumothorax of much longer duration the percentage of successful reinductions would be smaller aside from the greater liability of these cases to massive effusions, exudative pleurisies and empyemata.

Since the duration of pneumothorax is usually longer than the patient's stay in a sanatorium, the decision as to when inflation should be discontinued rarely falls to the lot of the sanatorium staff who established it.

A survey of our records confirms the statement made by Zambianchi (7) and by Bluhm (11), that of the numerous patients treated with pneumothorax very few return with indications for reinduction. This may be due to several causes: namely, the majority of patients probably get well and stay well, some are continued indefinitely, some show progression

in the opposite lung or develop complications, which may contraindicate pneumothorax. It is also probable that in some cases, particularly in the type reported by Rubin (2) and Mantoux (9), or similar to our cases *2* and *7*, reinduction is not attempted because the history of a previous pneumothorax and the roentgenological appearance of the chest make successful recollapse seem unlikely.

We share with the rest the fear of losing the pleural space and finding ourselves helpless before a reactivated lesion with thoracoplasty as the only other alternative. We, therefore, hesitate to take the responsibility and later on possibly feel guilty of having discontinued pneumothorax prematurely. Hence the percentage of patients on whom reinduction is more likely, namely, those in whom pneumothorax was discontinued voluntarily, is very small.

The longer pneumothorax is continued the greater are the chances for the development of complications, which are responsible for the formation of adhesions.

We reasoned, therefore, that it would be of some advantage to the patient not to continue pneumothorax much beyond the stage of clinical recovery and to terminate it voluntarily with a fair chance that, should it become necessary in the future, recollapse may be possible.

The prevailing policy of basing the duration of pneumothorax on the accepted criteria for minimal, moderately advanced or far advanced lesions and on the presence or absence of cavities is not entirely satisfactory. The important points to bear in mind are not so much the extent of the lesion as the age and type of it. We know that exudative lesions of more or less recent origin in young people have a strong tendency to heal by resolution in a considerable percentage of cases and that large cavities in this type of case frequently disappear in a surprisingly short time. We would, therefore, expect that recovery under pneumothorax treatment would also be more rapid in this type of case than in those with productive lesions and thick-walled cavities.

In managing our pneumothorax patients on whom this experiment was tried out we, therefore, bore in mind constantly the type and age of the lesion for which pneumothorax was induced and on the basis of clinical recovery we tried to estimate the probability of anatomical recovery. We used as a basis to judge clinical recovery the principles adopted by the National Tuberculosis Association for the estimation of an arrested case, namely, that all constitutional symptoms should be absent, and sputum, if any, microscopically free from tubercle bacilli for six months,

during the last two of which the patient has been taking one hour walking exercise twice daily or its equivalent. In addition we also required that the red blood sedimentation rate should be normal all this time. When this stage in the patient's condition was reached, we studied the X-ray findings to complete the picture. This was done by gradually diminishing the amount of air given at each inflation and by lengthening the periods between inflations. As the lung began to reëxpand and its structure came into view, the lesion, if any, became apparent. If the pathological condition, for which pneumothorax was instituted, was found to still be in need of collapse therapy, or if symptoms reappeared, the lung was immediately recollapsed. On the other hand, if the disease was found to be under complete control, the lesions either absorbed or fibrosed and the cavities obliterated, we could see no reason for continuing pneumothorax. It might seem futile to prolong this treatment merely as a prevention against possible reactivation. In such cases the lung was permitted to reëxpand entirely with the hope that, should there ever be a recrudescence of the disease, there is a fair chance in the light of our experience that reëstablishment of pneumothorax may be possible.

SUMMARY AND CONCLUSIONS

Eleven patients are reported in whom reinduction of pneumothorax was attempted 6 months to 4 years after the first pneumothorax was interrupted. In nine of these eleven, a free pleural space was found the second time and an effective pneumothorax was reëstablished in eight. (One did not require reinduction.)

One of these nine patients had bilateral pneumothorax in whom an effective collapse was secured on both sides the second time. We could not find a similar case reported in the literature.

Even though reinduction of pneumothorax was possible and an effective pneumothorax was obtained by us in nine out of eleven cases attempted, the fact that in eight of them reinduction was necessary on account of reactivation of lesion and return of symptoms convinced us that our first theory of basing the duration of pneumothorax on clinical recovery is not reliable and that pneumothorax should be continued much longer. However, the fact that pneumothorax could be successfully reinduced in such a high percentage of cases might help to dispel the universal fear of losing the pleural space when termination of pneumothorax becomes necessary or advisable for one reason or another.

Our experience also leads us to believe that when adhesions follow termination of pneumothorax they appear almost immediately upon re-expansion. On the other hand, if the lung does not become adherent immediately, it continues to remain free. The forces which are responsible for the formation of adhesions, operate most potently at the time of reëxpansion or immediately thereafter, and as the abnormal conditions brought about by the pneumothorax are removed and normal conditions in the pleural space return, it is natural to expect that the causes for the formation of adhesions will gradually disappear.

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ARTIFICIAL PNEUMOTHORAX REËSTABLISHED AFTER PHRENICOEXAIRESIS

WILLIAM C. VOORSANGER[1]

Since artificial pneumothorax was first introduced as a common procedure, chiefly through the efforts of Brauer and Spengler about 1900, both its technique and indications have undergone many changes.

We who have used pneumothorax for twenty-five years or more have seen the change from heavy trocars to fine light ones, from the operative sitting to the lying posture, from large initial doses (1,000 to 2,000 cc.) with attempts at immediate complete collapse to small initial doses with gradually extending intervals. In the application of artificial pneumothorax we have indeed made startling even though rather delayed advances. It started as a method for advanced hopeless cases, often as a mere palliative to control cough. In rapid succession we see the method extended in use to unilateral cavitation, then unilateral lesions of all kinds, then beginning lesions and final bilateral tuberculosis. The last named application is rapidly becoming popularized and may prove a boon to patients formerly condemned to a fatal termination. The method is naturally fraught with some risk but the often sudden and dramatic success attendant upon collapse of both lungs, especially in the presence of multiple cavitation, justifies its use.

Recompression or reëstablishment of artificial pneumothorax after a lung has completely reëxpanded has been seldom attempted. The doctrine has become rather fixed that, with reëxpansion, fibrosis, adhesions and obliteration of the pleural space develop. Therefore, when disease recurs in the reëxpanded lung we have assumed that thoracoplasty is the only remedial procedure left. Consequently it surprises us greatly that we can sometimes recompress, months or even years after reëxpansion. True in the majority of cases we fail, but we are most culpable if we do not at least attempt recompression, not once but several times before conceding failure. There are difficulties and perhaps dangers. Personally, I have found great difficulty and most often failure in at-

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tempting to administer air after a spontaneous pneumothorax. There seems to be no good reason why after a lung is spontaneously collapsed and starts to reëxpand we cannot administer enough air to keep this lung compressed, but such is the case at least in my own experience. This does not, however, deter me from attempting to keep up pneumothorax in this class of case until I am sure I fave failed.

The literature of the past ten years does not contain many reports of attempts at recompression. Pearson (1) in 1919 reported reëstablishment of pneumothorax after a two years' interval. Burnand (2) in 1921 quotes Dumarest "as successful in inducing a second pneumothorax after six months, but a third attempt a year later failed." Burrell (3) in 1922 reported success in a patient seven months after the last refill and in two others he failed to reproduce any pneumothorax twenty months and twelve months after cessation of treatment. Hutchinson (4) in 1925 reëstablished pneumothorax after an interval of six years and three months. Geer (5) reports a case in which "it was possible after the lung had come out to the chest wall to introduce 1,300 cc. of air." Morriss (6) in 1924 after a ten months' interval reëstablished collapse. More recently, cases of reëstablished pneumothorax have been reported by Mullen (7), Longo (8), Mantoux (9), Woodward (10), and Haensel (11) who describes three cases in which preliminary exairesis of the phrenic nerve allowed successful induction of pneumothorax previously unobtainable because of pleural adhesions. Rubin (12) reëstablished pneumothorax after an interval of four years. The patient, however, developed general miliary tuberculosis and died. His observations are worthy of comment. Rubin believes that more instances of reestablished pneumothorax would come to light if attempts were made more frequently. He states in conclusion, "on the other hand, instances are legion in which artificial pneumothorax cannot be reëstablished in patients who show neither clinically nor roentgenologically evidences of pleural symphysis. One must conclude that the only method of ascertaining whether a pleural space is free or obliterated is by inserting a needle attached to a manometer."

I am wholly in accord with Rubin, as the case report which follows will demonstrate. Less persistence in attempting recompression would have caused a wide-spread tuberculosis with fatal termination. That phrenicectomy materially aided in permitting recompression cannot be doubted.

Case Report

D. M., age 20, occupation, private secretary, entered Oaks Sanitarium December 18, 1929 complaining of cough, bloody expectoration and loss of weight. She had also been hoarse for several weeks. In August, 1929, she had influenza followed by pneumonia in October. She gave up her occupation owing to her constant and severe cough. This patient was brought to my office with an X-ray diagnosis of abscess at the base of the right lung. The original examination showed the following: Her weight was 131½ pounds, she was well nourished, and spoke with hoarse voice. There was no enlargement of lymph nodes. The tongue was coated; the pharynx was clear. Laryngeal examination showed marked reddening and swelling of the epiglottis and arytenoids. The left chest moved more than the right; there was dulness over the right base where one heard roughened breathing with inspiratory râles. Under the left clavicle there was roughened inspiration. Blood pressure was 120/90. Temperature ranged from 99° to 101°F. Pulse averaged 90. X-ray examination showed a fairly large cavity at the right base resting on the diaphragm and close to the mediastinum (figure 1). The blood showed secondary anaemia with a haemoglobin of 75 per cent. The sedimentation test index was 27 mm. The sputum measured about three ounces in twenty-four hours; it was foul smelling and contained numerous tubercle bacilli. Urine was normal.

The diagnosis thus was clearly one of basal tuberculosis with practically no involvement anywhere else in either lung. The character of the sputum, however, was proof that considerable destruction was taking place in the lung tissues. The patient was put to bed under absolute rest. She seemed to improve somewhat at first but on February 7, 1930 her evening temperature rose to 101.6°F. and persisted at 102°F. for several weeks. There ensued a series of haemoptyses, culminating, February 21, in the loss of twelve ounces of blood. On March 5 haemoptysis had subsided and the temperature became normal.

The first pneumothorax was induced on March 8, 1930 (figure 2). Air was given at intervals of two to three days for two weeks, then at intervals of a week, in amounts ranging from 200 to 500 cc., the average being 400 cc., until complete collapse was obtained when the interval was gradually increased to four weeks. She made excellent progress, had no more haemoptyses, was discharged from the Sanitarium June 24, 1931 and returned to her home to receive ambulant treatment. Her sputum became negative October 16, 1930. Her weight increased to 145 pounds, but remained stationary at 137 pounds. On January 3, 1932, there being no evidence of disease, the pneumothorax was discontinued and the lung allowed to expand (figure 3). We felt that we had accomplished a definite result, collapsing a lung with an acute exudative lesion for which both phrenicectomy and thorocoplasty had been advised and refused.

Although this patient remained comparatively well she still had a morning cough which, at times, showed streaks of blood and the sputum still had considerable odor, although it did not contain tubercle bacilli. In April, 1932, she contracted influenza and again began to cough and expectorate considerably. She returned to the Sanitarium May 27, 1932. Her sputum had again become poistive. She was losing weight and had afternoon temperatures usually around 99.8°F. Examination at this time showed (figure 4) that another cavity had formed at the right base just above the site of the former cavity. Pneumothorax was again attempted but unsuccessfully. Thorocoplasty was considered, and with this in mind a preliminary phrenico-exairesis was performed, June 24, 1932 in the usual way. Following this the patient did fairly well, cough subsided, and the temperature dropped to normal. The patient was again discharged from the Sanitarium August 15, 1932. She continued to cough, however, particularly in the morning when paroxysms would be quite violent, and the sputum was rather purulent in character; it again, however, became negative. After a short period of well-being at home she began to lose weight gradually, to get dyspnoeic, to run afternoon fever, and X-ray pictures taken at this time showed the formation of a third cavity high up in the centre of the right lung near the periphery (figure 5). Again thorocoplasty was advised and refused.

With little hope of success it was decided to attempt the reëstablishment of pneumothorax. The first attempt in the sixth interspace in the anterior axillary line failed, but the next day, February 5, 1933, pneumothorax was successfully reëstablished, with an initial dose of 250 cc. of air. This was repeated on February 8, 350 cc. of air being given. This pneumothorax was continued successfully at weekly intervals with 300 to 400 cc. of air until April 2, 1933 when the patient was discharged to her home and placed on ambulant treatment. Her sputum at this time was negative, she weighed 131½ pounds, had no cough and only slight expectoration. The right lung was completely collapsed with a pressure of plus two. The weekly interval was maintained until May 22, 1933, then extended to ten days until February 8, 1934, when the interval was extended to two weeks. This was continued until March 7, 1935, when the interval was extended to three weeks. By November 21, 1935 the patient was feeling well; she had no cough nor sputum; her sedimentation index was 9 mm.; and she was working at her occupation a full day without tiring. Therefore it was decided to cease pneumothorax treatment. The X-ray report of January 16, 1936 stated: "Thickening of right pleura; slight displacement of heart and mediastinum to right; fibrotic changes in right upper lobe with no evidence of active disease." After ten months of daily work the patient is symptom-free and weighs 151 pounds. (See figures 6, 7, 8 & 9.)

COMMENT

This case is unusual: First, because it began with an acute exudative lesion at the right base which was roentgenologically considered to be an abscess of the lung until tubercle bacilli found in the sputum established the correct diagnosis.

Second, it was the type of tuberculosis that probably would not have been cured by thoracoplasty, since being exudative in character the lesions were apt to recur and did so. We saw two subsequent cavities after the first developed while the patient was under observation. The X-ray pictures clearly demonstrated that these cavities were new cavities and not a reopening of the original cavity.

Third, the case represents a rather stormy course of six years' duration during which time absolute coöperation of doctor and patient were necessary to achieve results. The first recovery was probably never quite complete since cough and sputum persisted after the lung was allowed to expand. The X-ray picture however taken at this time showed a complete fibrosis at the base of the lung with no evidence of cavitation. When, after repeated attempts, pneumothorax could not be reëstablished phrenic evulsion was done with the intention of performing a thoracoplasty later on. It was certainly startling and rather dramatic not only to be able to reëstablish pneumothorax after the phrenic-nerve operation, but to produce a complete collapse in a very short time which was far better than the original one. We attribute our success in reëstablishing pneumothorax to the phrenicoexairesis. We do not believe we could have accomplished our result without it.

CONCLUSION

This case has been reported in detail to demonstrate that artificial pneumothorax can be reëstablished and that it should be more often attempted, particularly after phrenic paralysis.

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PLATE 1

Fig. 1. December 12, 1929. Cavity at right base.

Fig. 2. May 3, 1930. Artificial collapse of right lung.

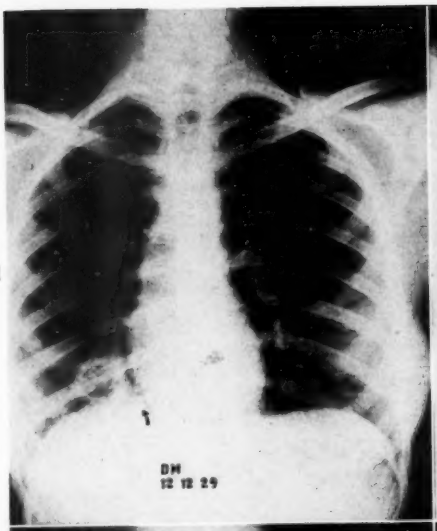
Fig. 3. March 24, 1932. Reëxpanded right lung after first pneumothorax. Fibrosis in upper part of right lung; apparently healed area at base.

Fig. 4. July 23, 1932. Second cavity at right base above the site of the original cavity.

Fig. 5. June 14, 1932. Six months after phrenicoexairesis a cavity appeared high up in the lung in the fourth and fifth interspaces.

Fig. 6. May 23, 1933. Recollapse of the right lung successfully performed. Small fluid level at base.

Fig. 1



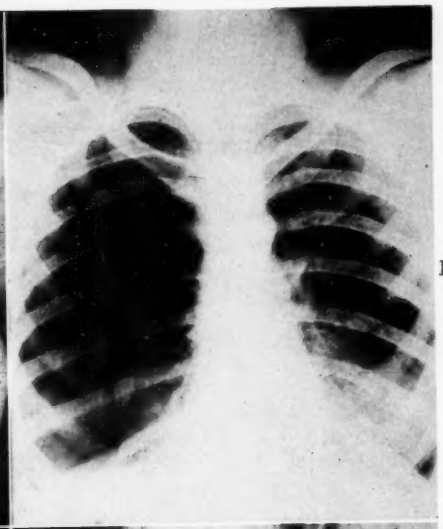
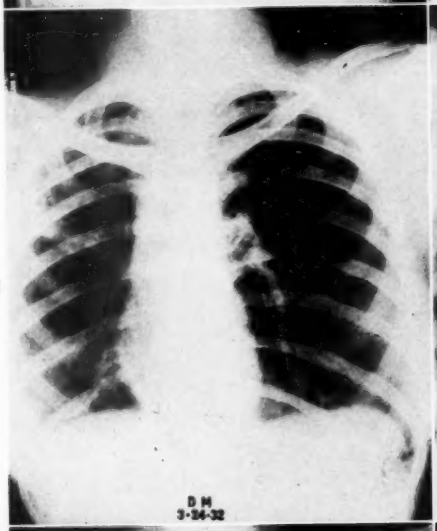


Fig. 2

Fig. 3



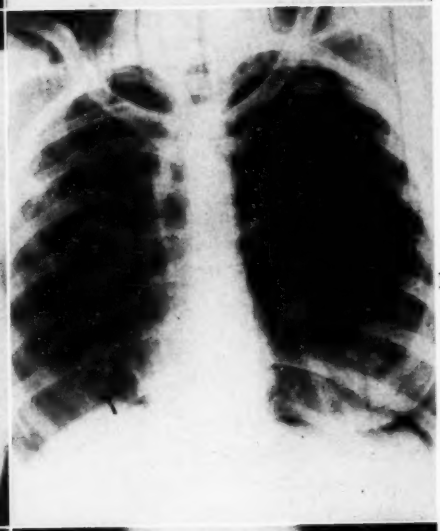
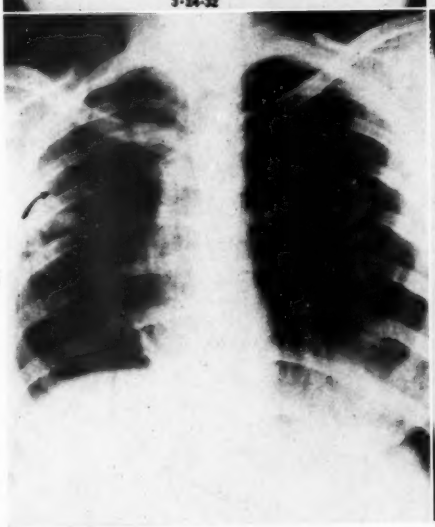


Fig. 4

Fig. 5



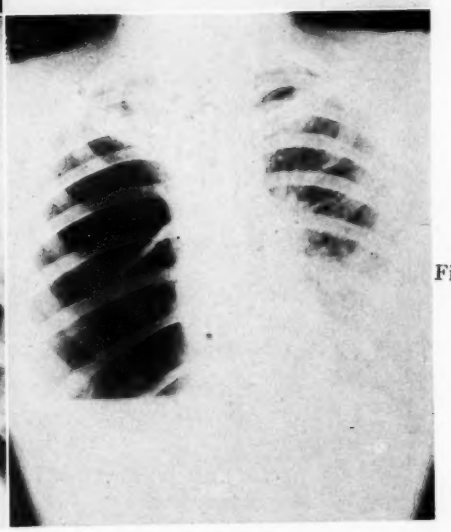
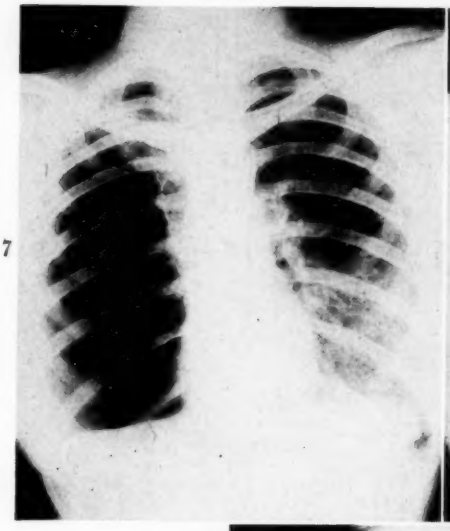


Fig. 6

PLATE 1

Fig. 7



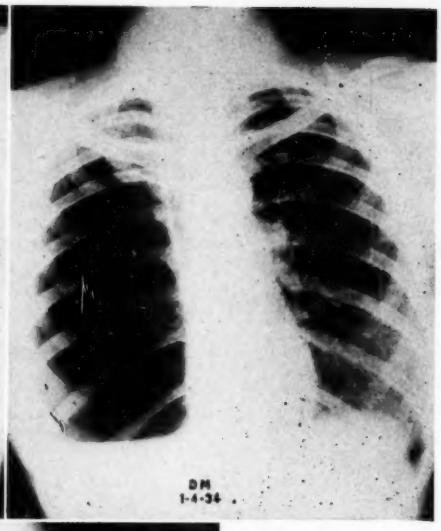


Fig. 8

Fig. 9

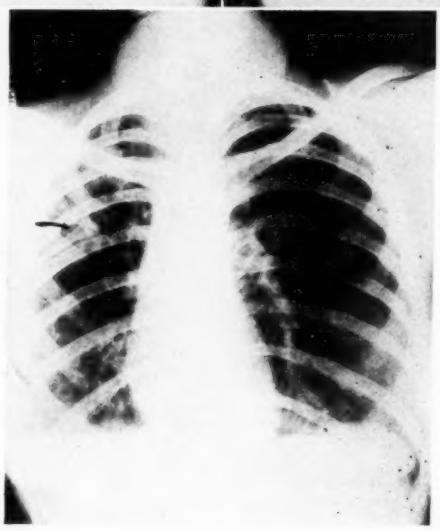


PLATE 2

Fig. 7. August 24, 1934. Another view of right lung collapsed. Picture taken on inspiration.

Fig. 8. January 4, 1934. Right lung fully collapsed with small fluid level at base.

Fig. 9. January 16, 1936. Right lung fully expanded. No evidence of cavity. Small fibrous area in second interspace arteriorly at site of the former cavity. Left lung apparently clear.

TRAUMA AS A FACTOR IN POTT'S DISEASE

MAX H. SKOLNICK

The relationship of trauma to tuberculosis of the spine deserves consideration and attention. In our present stage of industrial development, this aspect is assuming an important phase in the proper medico-legal disposition of such problems. To be sure, many cases of tuberculosis have been brought forth in which trauma was supposed to have been the precipitating cause of the disease, but in which it had only played a revealing rôle. In such cases, tuberculosis was fully developed prior to the trauma, and therefore had existed independently.

On the other hand, a direct relationship between trauma and tuberculosis can definitely be ascertained to exist under certain conditions. By understanding the nature of tuberculosis, it can readily be demonstrated how this effect may take place. After the entrance of the tubercle bacillus in the body, the organisms may circulate in the blood and a trauma may determine the implantation and growth at the site of the trauma. The focalization of the tubercle bacillus is known to be prone to develop under such circumstances in which the soil is so prepared. Trauma may influence the development of tuberculosis either by the actual liberation of the bacillus from a previously latent focus or by injuring the tissues, thus creating a site of lowered resistance.

This assumes major importance when it is remembered that a large percentage of adults harbor the tubercle bacillus during their lifetime. The foci of the organism may be present in any site of the body; however, it is most commonly found in the lymph nodes and the lungs. Postmortem statistics repeatedly show the presence of the tubercle bacillus existing in apparently latent foci.

On the other hand, trauma may not always produce the development of the disease tuberculosis, especially as it affects the bones and joints. Peculiarly enough, severe trauma is almost completely without incidence in precipitating tuberculosis. The reasons proposed to explain this phenomenon are twofold: (1) An overwhelming response of the circulation with the repair elements of the blood predominating is not conducive to the deposit of the tubercle bacillus, and (2) immediate medical atten-

tion is provided in severe injuries in which the body is at optimum rest, whereas neglect of proper care usually follows less severe injuries.

The appearance or recognition of clinical findings of a resultant tuberculosis of the bones and joints, especially in an involvement of the spinal column, may not be evident for varying lengths of time. Tuberculosis of the bones is known to be a chronic destructive disease. In some cases, months or years may elapse before the disease is recognized. Even after tubercle bacilli have entered a site of lowered resistance, various stages of activity may delay the development of bone destruction, so that progress may be slow and the patient may be practically symptomless for a considerable length of time. Adults who were previously in apparently perfect health prior to an injury may not rapidly develop the signs and symptoms of Pott's disease.

The diagnosis of Pott's disease may not be made until the late stages of deformity and the complications of abscess or paralysis are present. The symptoms of the patient should not be relied on entirely as a lead to the diagnosis in cases of trauma to the bones and joints. Roentgen rays should be employed as an irreplaceable aid to diagnosis.

Thus our modern medical problem is to recognize the rôle trauma may play in the aetiology of tuberculosis of the bones and joints. Slight or moderately severe injuries may be an important factor in tuberculosis of the bones, in which the course of development may be either slow and insidious, or culminating. Early recognition may allow the immediate installation of treatment with a possible avoidance of the otherwise inevitable deformities and complications.

The following case is presented to illustrate the importance of trauma as a factor in the precipitation of Pott's disease. In this case, the diagnosis was delayed until the late stage of the disease was developed with bone deformity and abscess formation as complications.

Case Report

H. E., white, male, age thirty-four, a fireman by occupation. The patient states that he was in apparent perfect health up to the time of an accident on November 24, 1930, while responding to an alarm at night at the fire station. While in the usual position on the pole at the sleeping quarters, in the act of sliding down and after partly through the floor hole, the patient was unexpectedly struck by the left trap-door, which was bumped back towards the floor hole. The patient continued in his descent, somewhat off balance, to the ground floor, along with parts of the trap-door which was broken by the force

and contact with his body. He was so excited and disturbed by this unusual accident that he was unable to realize the total extent of the immediate injuries he suffered in the accident. His first pain came from his left lower chest and back regions. However, upon questioning, he did not admit severe suffering at that time. Nevertheless, some hours later, he complained of girdle-type shooting pains in the lower rib region, radiating from his spine to the anterior chest-wall. He started his furlough at this time, and because of discomfort and pain, he was forced to remain in bed for about seven days. At the end of that time, he sought medical advice of the department physician, as the severity of the discomfort did not lessen. X-ray pictures of the ribs were taken on the physician's advice, and these did not show any abnormality. Because of his continued physical incapacity, he was returned to duty as a house watchman for the next few weeks, after which time he resumed regular duty. The discomfort and back pain at this time was beginning to improve somewhat. This relative freedom from severe distress lasted over a period of about three years, although even during this period he was not at any time in his best physical condition. Following this period of relative remission, his disability gradually increased in severity with exaggerations of weakness, tiredness and back pains. At first he would experience some relief with aspirin and similar drugs, but they became gradually less effective. His pains persisted with a girdle-like type of distribution, being more severe at intervals, especially after doing heavy work while on duty. He finally sought medical aid again, and was seen in January, 1935, by the department physician, who thought he had pleurisy. Medical treatments along this line did not bring about any relief to the patient. He sought other medical opinions, which were different in diagnosis and treatment, leaving the patient still unrelieved. His lungs were X-rayed and his sputum was examined but these were found to be negative for tuberculosis. By November, 1935, the patient's disability due to back pain and weakness had progressed so far that he made a special effort to enter the University Hospital at Ann Arbor for a complete medical examination. He was hospitalized at Harper Hospital for treatment on November 27, 1935, being admitted by ambulance on a stretcher. His previous history was not contributory.

X-ray examinations made at Ann Arbor University Hospital on November 15, 1935, were reported as follows: "No abnormality of the bony cage. Lung fields clear bilaterally. Hip, sacro-iliac, and lumbosacral joints normal. Lumbar spine not unusual. Destructive process in the dorsal spine of the eighth and ninth bodies with a kyphosis at this level, with a rather prominent paravertebral shadow. Impression: Tuberculosis of the anterior margin of the eighth and ninth dorsal vertebral bodies, accompanied by a paravertebral abscess."

Laboratory examinations did not reveal any pertinent data.

Based on the history, physical examinations, and X-ray examinations, the diagnosis of Pott's disease with the complication of abscess formation was made.

DISCUSSION

This patient was in apparent perfect health previous to an injury which he received while on duty as a fireman. This injury was not severe. The final diagnosis was made after a considerable delay, inasmuch as definite well-advanced bone deformities of his spine were present, with the complication of abscess formation. The patient apparently underwent an early symptomless course of this disease attended by a slowly progressing process until the well-advanced stage with typical symptoms was present. Therefore trauma was the predisposing factor in the development of Pott's disease in this case.

Medical authorities substantiate the opinion that trauma may act as the precipitating cause of Pott's disease and other tuberculous involvements of the bones and joints.

Kessler (4) points out that tuberculosis of the bones is a slow developing disease, on which it is impossible to set a time limit. He shows that it is very possible for an injured worker with very extensive disease of the spine to continue at work, and even at laborious work. Thus the condition of tuberculosis of the spine, although present and active, may not be diagnosed for a considerable period of time following the injury.

May (6) cites a case of a worker who slipped, twisted and bumped his knee in which swelling appeared after a very short interval. The patient remained in bed for some time, thereafter returning to his work apparently well. However, after a considerable time had elapsed, symptoms appeared and his injured joint was diagnosed as tuberculous. A review of the case showed that the individual was in previous good health, but following this slight injury he consequently developed poor health with a period in between of comparative freedom from symptoms.

Fraser (2), in an extensive review of the subject in which he cites such authorities as Choyce, Jones, Lewis, Goldthwait, Susewind, and others, writes that cases frequently occur in which persons of previously good health, without any history of tuberculosis, develop Pott's disease as a consequence of trauma. In addition, attention is called to the fact that there is often a considerable interval between the trauma and the beginning of symptoms. He emphasizes that no small degree of importance should be attached to this fact of delayed manifestations of tuberculosis. Several years may elapse after an injury before the condition is clinically

recognized. An instance is reported in which five years had passed from the time of the trauma until a clinical diagnosis of Pott's disease was made. Another case is cited of a laborer, twenty-three years of age, who was struck by the crank of a truck over the lower part of his right patella. No wound nor any discoloration of the subcutaneous tissues was evident. The bone began to be painful about one week following the injury, but in spite of this he continued to work for a period of months. At this time, he sought medical advice, and was informed that no bone lesion was present. However, his condition became aggravated. He again sought medical advice after a considerable period in which his disability became progressively almost complete. After this delay the condition of tuberculosis of the bone was diagnosed. His symptoms had preceded this diagnosis for a considerable time.

Mock (8) reiterates that there is a definite relationship of injuries to the chest and the development of tuberculosis, especially in the bones of the spine. He cites several cases of injury to the chest in men who later were found to have tuberculosis of the bones, whereas previous to the injury there was no evidence of the disease. Thus trauma could act as a very definite predisposing cause of tuberculosis of the bones.

Goldthwait, Painter and Osgood (3) collaborate in their discussion on the causal relationship of trauma and Pott's disease. Besides the effect of contagion and heredity, they state that trauma plays an important rôle. There are only a few cases in which a history of trauma is not obtained. Moreover, there may often be a considerable interval between the trauma and the beginning of symptoms. Because of the insidious development, the patient is usually able to work, suffering only moderate discomfort, until the symptoms gradually become more pronounced. The complications of abscess and paralysis are much more likely to develop if diagnosis and treatment are delayed.

Whitman (9) states that although Pott's disease is known to be a chronic destructive process of the bodies of the vertebrae, modern methods should be used for the early detection of the disease before the entire development of symptoms is evident. By this means, the deforming effects may be checked and even prevented by timely treatment. The disease may undergo various stages of development, in which there is a marked resistance to its progress. If undiscovered the disease will slowly advance, with intermittent periods of quiescence, until there may be an exacerbation of symptoms with the formation of deformities and

complications. Thus an early diagnosis is essential for a good prognosis.

Davis (1) states that injury may play a conspicuous part in the pathogenesis of Pott's disease by providing a suitable soil for the tubercle bacillus. The affection does not appear to start from severe injuries, but from slight ones that cause but little disability at the time of their occurrence. The onset of tuberculosis of the bone is very often extremely insidious, and it may be only after a considerable time that the symptoms become at all marked. Thus early diagnosis may be difficult if too much reliance is placed on symptomatology. In some cases, the characteristic symptoms are totally absent, even though the disease is steadily advancing.

Kite (5) is also of the opinion that trauma plays a definite rôle in the development of Pott's disease, as well as tuberculous involvements of other bones and joints. He states that a definite history of an injury to the osseous system may be generally obtained preceding the onset of the disease. Animal experiments have proved the fact that an injured bone or joint will develop tuberculosis more readily than an uninjured one.

SUMMARY

1. Trauma is a definite factor in the pathogenesis of Pott's disease.

2. A tuberculous infection may be altered from its apparently harmless latent course into one of activity as the result of an adequate trauma.

3. The development of tuberculosis of the bones seems to be preceded more frequently by slight or moderate trauma than by violent trauma.

4. A considerable length of time may elapse between the trauma and the recognition of the disease, particularly since the development of symptoms may be very slow.

5. Too often the diagnosis of Pott's disease is made at a late stage when deformities and complications are present. Symptomatology alone forms an inaccurate guide for the early recognition of the disease. Roentgen rays, especially in the absence of the usual symptoms, are necessary for the recognition of the early stages.

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PLEURAL FLUID IN THE COURSE OF ARTIFICIAL PNEUMOTHORAX [1, 2]

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Part 1

JOHN M. NICKLAS

The following statistics represent the findings in a study of 375 patients with therapeutic pneumothorax, the majority of whose treatment was begun during the past three years. Only the basic data which we have collected will be presented.

These data deal with two groups of cases: the first, treated prior to July 7, 1935, by what is known as the standard method of treatment in use in most sanatoria; and the second, treated following July 7, 1935, by a new method (1).

By the standard method is meant the giving of pneumothorax refills not oftener than twice a week during the period of active collapse of the tuberculous lung. By the new method is meant the giving of daily refills until a satisfactory collapse of the involved part of the lung is obtained, pneumothorax is found to be a therapeutic failure or until dyspnoea, loss of weight and other constitutional findings necessitate a lengthening of the course of treatment.

The data also deal with two main groups of fluids which we divide into "hot" and "cold" effusions. By "hot" effusions we mean those fluids having a definite symptom complex with fever reaction; whereas, by the "cold" effusions we mean those fluids which do not have a definite symptom complex or a concurrent rise in temperature. Both this and the preceding definition have been used at this point in the discussion in order to clarify the presentation of the statistics which follow. They represent the results of long study and observation and reference will be made to them in our conclusions and elsewhere in more detail.

In Part 1 of this discussion I shall present the statistics which bear

[1] From the Tuberculosis Division of Grasslands Hospital, Valhalla, New York.

[2] Presented at the Clinical Session on Chronic Pulmonary Diseases, Tuberculosis Sanatorium Conference of Metropolitan New York, Cornell University Medical College, New York City, October 7, 1936.

upon the occurrence of first effusions in pneumothorax with their aetiological factors, course and treatment. Dr. William A. Zavod will report upon the clinical manifestations and laboratory findings as related to the course of the so called "hot" and "cold" effusions in Part 2. Dr. R. Maxwell Franklin will briefly report in Part 3 upon the two methods of giving pneumothorax with the incidence of fluid, the average management of pleural fluids at Grasslands and a description of tube drainage (2) in our cases with empyema.

Review of the 375 pneumothorax cases discloses the following about color, sex and ages:

1: 295 (78.6 per cent) were white and 80 (21.4 per cent) colored, making a ratio of slightly less than four to one.

2: 151 (40.3 per cent) were males and 224 (59.7 per cent) females, making a ratio of approximately two to three.

3: 232 (61.8 per cent) were treated by the standard method. Of this series:

a. 88 (37.9 per cent) were males, 64 (72.7 per cent) whites and 24 (27.3 per cent) colored.
b. 144 (62.1 per cent) were females, 115 (79.9 per cent) whites and 29 (20.1 per cent) colored.

4: 143 (38.2 per cent) were treated by the new method. Of this series:

a. 63 (44 per cent) were males, 54 (85.7 per cent) whites and 9 (14.3 per cent) colored.
b. 80 (56 per cent) were females, 62 (77.4 per cent) whites and 18 (22.6 per cent) colored.

5: Approximately 60 per cent of each racial group were females.

6: The ages ranged from 3 to 72 years, the majority of the females being from 15 to 35 years and the males from 25 to 55 years. Distribution of the ages by decades elicits the following:

a. 66 (17.6 per cent) second decade
b. 162 (43.2 per cent) third decade
c. 82 (21.8 per cent) fourth decade
d. 42 (11.2 per cent) fifth decade
e. 244 (60.8 per cent) second and third decades
f. 310 (82.6 per cent) second, third and fourth decades
g. In the first decade there were 3 cases, and in the sixth, seventh and eighth decades 16, 3 and 1 respectively, making a total of 375 cases.

No aetiological factors of import were found pertaining to color, sex or age.

In studying the relation of the type and extent of pulmonary tuberculosis to the type of effusions, we find the following:

Incidence of first effusions:

1: 253 (67.5 per cent) of the pneumothorax cases had first effusions.
2: 122 (32.5 per cent) of the pneumothorax cases had no effusions.

Type incidence of first effusions:

1: 161 (63.6 per cent) of the first effusions (253) were cold effusions.
2: 92 (36.4 per cent) of the first effusions (253) were hot effusions.
3: 161 (43.0 per cent) of the pneumothorax cases (375) had cold effusions.
4: 92 (24.5 per cent) of the pneumothorax cases (375) had hot effusions.
5: 122 (32.5 per cent) of the pneumothorax cases (375) had no effusions.

Stage of disease (extent) and type incidence of effusions:

A.

1: 132 (35.2 per cent) of the pneumothorax cases (375) had moderately advanced pulmonary tuberculosis.

2: 83 (62.8 per cent) of the patients with moderately advanced pulmonary tuberculosis had first effusions:

a. 63 (76.0 per cent) of the patients with moderately advanced pulmonary tuberculosis with first effusions had cold effusions and 20 (24.0 per cent) of them had hot effusions.

3: 63 (47.7 per cent) of the patients with moderately advanced pulmonary tuberculosis (132) had cold effusions, 20 (15.1 per cent) had hot effusions and 49 (37.2 per cent) had no effusions.

B.

1: 243 (64.8 per cent) of the pneumothorax cases (375) had far advanced pulmonary tuberculosis.

2: 170 (70.0 per cent) of the patients with far advanced pulmonary tuberculosis had first effusions:

a. 98 (57.6 per cent) of the patients with far advanced pulmonary tuberculosis with first effusions had cold effusions and 72 (42.4 per cent) of them had hot effusions.

3: 98 (40.3 per cent) of the patients with far advanced pulmonary tuberculosis (170) had cold effusions, 72 (29.6 per cent) had hot effusions and 73 (30.1 per cent) had no effusions.

Type and extent of pulmonary tuberculosis with type incidence of first effusions:

Acute Cases—All Stages of Tuberculosis

A.

1: 143 (38.1 per cent) of the pneumothorax cases (375) had acute disease.

2: 103 (72.0 per cent) of the cases with acute pulmonary tuberculosis (143) had first effusions:

a. 57 (55.3 per cent) of the cases with acute pulmonary tuberculosis with effusions had cold effusions and 46 (44.7 per cent) of them had hot effusions.

3: 57 (39.9 per cent) of the cases with acute pulmonary tuberculosis had cold effusions, 46 (32.1 per cent) had hot effusions and 40 (28.0 per cent) had no effusions.

Acute Cases—Moderately Advanced Tuberculosis

B.

1: 40 (30.3 per cent) of the cases with moderately advanced pulmonary tuberculosis (132) had acute disease.

2: 29 (72.5 per cent) of the cases with acute moderately advanced tuberculosis (40) had first effusions:

a. 21 (72.4 per cent) of the cases with acute moderately advanced tuberculosis with effusions had cold effusions and 8 (27.6 per cent) of them had hot effusions.

3: 21 (52.5 per cent) of the cases with acute moderately advanced tuberculosis had cold effusions, 8 (20.0 per cent) had hot effusions and 11 (27.5 per cent) had no effusions.

Acute Cases—Far Advanced Tuberculosis

C.

1: 103 (42.4 per cent) of the cases with far advanced pulmonary tuberculosis (243) had acute disease.

2: 74 (71.8 per cent) of the cases with acute far advanced tuberculosis (103) had first effusions:

a. 36 (48.6 per cent) of the cases with acute far advanced tuberculosis with effusions had cold effusions, and 38 (51.4 per cent) had hot effusions.

3: 36 (34.9 per cent) of the cases with acute far advanced tuberculosis had cold effusions, 38 (36.9 per cent) had hot effusions and 29 (28.2 per cent) had no effusions.

Chronic Cases—All Stages of Tuberculosis

D.

1: 232 (61.8 per cent) of the pneumothorax cases (375) had chronic disease.

2: 150 (64.6 per cent) of the cases with chronic pulmonary tuberculosis (232) had first effusions:

a. 104 (69.3 per cent) of the cases with chronic pulmonary tuberculosis with effusions had cold effusions and 46 (30.7 per cent) of them had hot effusions.

3: 104 (44.8 per cent) of the cases with chronic pulmonary tuberculosis had cold effusions, 46 (19.8 per cent) had hot effusions and 82 (35.4 per cent) had no effusions.

Chronic Cases—Moderately Advanced Tuberculosis

E.

1: 92 (69.7 per cent) of the cases with moderately advanced tuberculosis (132) had chronic disease.

2: 54 (58.7 per cent) of the cases with chronic moderately advanced tuberculosis (92) had first effusions:

a. 42 (77.7 per cent) of the cases with chronic moderately advanced tuberculosis with effusions had cold effusions and 12 (22.3 per cent) of them had hot effusions.

3: 42 (45.7 per cent) of the cases with chronic moderately advanced tuberculosis had cold effusions, 12 (13.0 per cent) had hot effusions and 38 (41.3 per cent) of them had no effusions.

Chronic Cases—Far Advanced Tuberculosis

F.

1: 140 (57.6 per cent) of the cases with far advanced tuberculosis (243) had chronic disease.

2: 96 (68.6 per cent) of the cases with chronic far advanced tuberculosis (140) had first effusions:

a. 62 (64.6 per cent) of the cases with chronic far advanced tuberculosis with effusions had cold effusions and 34 (35.4 per cent) of them had hot effusions.

3: 62 (44.3 per cent) of the cases with chronic far advanced tuberculosis had cold effusions, 34 (24.3 per cent) had hot effusions and 44 (31.4 per cent) had no effusions.

The primary effusions were classified as: (*1*) cold effusions comprising 123 small and 38 large fluids without fever, and (*2*) hot effusions comprising 92 large fluids with fever.

A larger number of cold effusions were found among the females whereas the distribution of hot effusions was equal in both sexes.

The greatest number of acute cases were found among the males and the largest number of chronic cases among the females.

The more advanced and acute the disease, the greater the incidence of fluid.

Generally speaking, one would anticipate with the acute lesions of the lung a greater incidence of fluid, especially empyemata, and in our series this has been proved. Experience has taught us that much consideration must be given to the method of treatment in these acute lesions.

In determining the relative merits of the two methods of treatment, I have reviewed the statistics pertaining to the time of incidence and the type of fluid in relation to the duration of pneumothorax and the following is elicited:

Duration of pneumothorax treatment (375 cases):

1: 94 (25.0 per cent) less than six months
2: 74 (19.8 per cent) between six months and one year
3: 86 (22.9 per cent) between one and two years
4: 47 (12.5 per cent) between two and three years
5: 74 (19.8 per cent) over three years

Relation of type of first effusion to month of incidence during pneumotherapy:

Incidence of Cold Effusions during Pneumothorax

One hundred and sixty-one (63.6 per cent) of the pneumothorax cases with effusions (253) had cold effusions; the time of their occurrence was as follows:

1: 46 (28.6 per cent) first month
2: 30 (18.7 per cent) second month
3: 17 (10.6 per cent) third month
4: 6 (3.7 per cent) fourth month
5: 19 (11.8 per cent) fifth month
6: 8 (4.9 per cent) sixth month
7: 24 (14.9 per cent) second half of year
8: 11 (6.8 per cent) after one year
9: 93 (57.7 per cent) first three months
10: 126 (78.2 per cent) first six months
11: 150 (93.1 per cent) first year

Incidence of Hot Effusions during Pneumothorax

Ninety-two (36.4 per cent) of the total effusions (253) were hot effusions; their time of occurrence was as follows:

1: 19 (20.7 per cent) first month
2: 23 (25.0 per cent) second month
3: 16 (17.4 per cent) third month
4: 5 (5.4 per cent) fourth month
5: 6 (6.5 per cent) fifth month
6: 4 (4.35 per cent) sixth month
7: 15 (16.3 per cent) second half of year
8: 4 (4.35 per cent) after one year
9: 58 (62.9 per cent) first three months
10: 73 (89.0 per cent) first six months
11: 88 (95.6 per cent) first year

Incidence of All Effusions (253)

1: 151 (59.6 per cent) first three months
2: 199 (78.5 per cent) first six months
3: 233 (92.0 per cent) first year of pneumothorax

Incidence of First Effusions during Pneumothorax Treatment by Standard Method

1: 232 (61.8 per cent) of the pneumothorax cases (375) were treated by the standard method:

a. 176 (75.9 per cent) developed effusions.
b. 56 (24.1 per cent) had no effusions.

2: 109 (61.9 per cent) of the cases (176) developing effusion had cold effusions and 67 (38.1 per cent) of them had hot effusions.

The time of occurrence of the 109 "cold" effusions in the group of patients treated by the standard pneumothorax method was as follows:

1: 28 (25.7 per cent) first month
2: 21 (19.3 per cent) second month
3: 13 (12.0 per cent) third month
4: 2 (1.8 per cent) fourth month
5: 12 (11.0 per cent) fifth month
6: 7 (6.5 per cent) sixth month
7: 15 (13.7 per cent) second half of year
8: 11 (10.0 per cent) after one year
9: 62 (58.6 per cent) first three months

10: 83 (74.3 per cent) first six months
11: 98 (90.0 per cent) first year

The time of the occurrence of the 67 "hot" effusions in the group of patients treated by the standard pneumothorax method was as follows:

1: 13 (19.4 per cent) first month
2: 15 (22.4 per cent) second month
3: 12 (17.9 per cent) third month
4: 1 (1.5 per cent) fourth month
5: 4 (6.0 per cent) fifth month
6: 4 (6.0 per cent) sixth month
7: 14 (20.8 per cent) second half of year
8: 4 (6.0 per cent) after the first year
9: 40 (59.7 per cent) first three months
10: 49 (73.1 per cent) first six months
11: 63 (94.0 per cent) first year

The time of the occurrence of all (176) effusions, "hot" and "cold," in the group of patients (232) treated by the standard pneumothorax method was as follows:

1: 102 (58.0 per cent) first three months
2: 132 (75.0 per cent) first six months
3: 161 (91.4 per cent) first year

Incidence of First Effusions during Pneumothorax Treatment by the New Method

1: 143 (38.2 per cent) of the pneumothorax cases (375) were treated by this method:

a. 77 (53.8 per cent) developed effusions.
b. 66 (46.2 per cent) had no effusions.

2: 52 (71.4 per cent) of the cases developing effusions had cold effusions and 25 (28.6 per cent) of them had hot effusions.

The time of the occurrence of the 52 "cold" effusions in the group of patients treated by the new pneumothorax method was as follows:

1: 18 (34.6 per cent) first month
2: 9 (17.3 per cent) second month
3: 4 (7.7 per cent) third month
4: 4 (7.7 per cent) fourth month
5: 7 (13.4 per cent) fifth month
6: 1 (2.0 per cent) sixth month
7: 9 (17.3 per cent) second half of year

8: 0 (0.0 per cent) after the first year
9: 31 (59.5 per cent) first three months
10: 43 (82.5 per cent) first six months
11: 44 (84.6 per cent) first year

The time of the occurrence of the 25 "hot" effusions in the group of patients treated by the new pneumothorax method was as follows:

1: 6 (24.0 per cent) first month
2: 8 (32.0 per cent) second month
3: 4 (16.0 per cent) third month
4: 4 (16.0 per cent) fourth month
5: 2 (8.0 per cent) fifth month
6: 0 (0.0 per cent) sixth month
7: 1 (4.0 per cent) second half of year
8: 0 (0.0 per cent) after the first year
9: 18 (72.0 per cent) first three months
10: 24 (82.5 per cent) first six months
11: 25 (84.6 per cent) the first year

The time of the occurrence of all effusions (77) in the group of patients treated by the new pneumothorax method was as follows:

1: 49 (63.6 per cent) first three months
2: 67 (87.0 per cent) first six months
3: 69 (89.6 per cent) the first year

The incidence of fluids is greater with the standard method of treatment (75.9 per cent against 53.6 per cent). (This, however, covers only one year of study with the new method.)

There is a greater incidence of fluid early in pneumothorax with the new method of treatment, whereas the fluids tend to occur later in the course of the old method of treatment.

The incidence of hot effusions (large fluids with fever) is quite high with the old method of treatment, especially in the acute cases.

The number of cases without fluid is greater under the new method during the first year of treatment.

The majority of fluids occurred during the first six months of pneumothorax therapy (59.6 per cent in the first three months; 92 per cent during the first year). Fluid occurrence with the old method in the first six months of treatment was 75 per cent, but with the new method the fluid occurrence was 87 per cent.

Fluid occurrence is greater in males during the early period of the

treatment, whereas it is greater in females during the latter period of treatment. It is often seen during the reëxpansion period.

Cold effusions occurred early in the pneumothorax treatment with both methods, whereas hot effusions occurred later in the treatment, especially with the standard method of treatment.

The later the appearance of fluid during the course of pneumothorax treatment, the greater was the liability of fluid with fever. This was especially true in males.

The new method of giving pneumothorax, to date, seems to favor the size or incidence of fluids, as noted. However, further study upon these points seems indicated. Notwithstanding, the good accomplished in establishing earlier knowledge about the success or failure of pneumothorax and the closure of cavities more than compensates for the added burden imposed upon the pneumothorax program in its initial stages under the new method.

The incidence of primary effusions by sex and side of chest in which they were found with pneumothorax therapy is as follows:

1: 105 (41.5 per cent) males had fluid, 52 (49.5 per cent) on the right and 53 (50.5 per cent) on the left.

2: 148 (58.5 per cent) females had fluid, 60 (40.5 per cent) on the right and 88 (59.5 per cent) on the left.

3: Of all fluids 112 were on the right, and 141 on the left side.

4: 71 males had fluid with the standard method of treatment; right, 35 and left, 36.

5: 105 females had fluid with the standard method of treatment; right, 40 and left, 65.

6: 34 males had fluid with the new method of treatment, 17 on either side.

7: 43 females had fluid with the new method of treatment; right, 20 and left, 23.

Thus we find a high incidence of female patients with fluids in the left pleural cavity; also a larger number of patients without fluid with the new method of treatment. However, the time factor in this new group of patients under treatment will, no doubt, change our deductions in the future.

The study of the effect of pressures upon the incidence of fluid elicited the following, in addition to points presented:[3]

[3] Definition of negative and positive intrapleural pressures: The corrected readings were taken with a U-tube water manometer while the patient was lying horizontally with the

Relation of type of effusion to intrapleural pressures:

1: 182 (48.5 per cent) of the pneumothorax series (375) had negative pressures; of these 74 (40.6 per cent) had no effusions, 88 (48.3 per cent) had cold effusions, 20 (11.1 per cent) had hot effusions, 108 (59.4 per cent) had effusions.

2: 193 (51.5 per cent) of the pneumothorax series had positive pressures; of these, 145 (75.1 per cent) had effusions; 48 (24.9 per cent) had no effusions; and 73 (37.8 per cent) had cold effusions, 31 (16.0 per cent) of these 73 cases were preceded by positive pressures and 42 (21.8 per cent) were followed by positive pressures.

3: 72 (37.3 per cent) of the cases with positive pressure had hot effusions; 36 (18.65 per cent) of these 72 cases were preceded by positive pressures and 36 (18.65 per cent) were followed by positive pressures.

There was a high incidence of cases without fluid noted with negative pressures and a higher incidence of fluid with positive pressures.

The number of cases with positive pressures after the presence of fluid in the pleural cavity is greater than the number found with positive pressures before fluid was present.

A point of considerable importance is the high incidence of hot effusions with positive pressures; 72 cases were found with positive pressures (36 before effusion and 36 after effusion), in contrast to 20 with negative pressures.

In addition, all of our empyemata arose from hot effusions.

We also find a larger number of small and large effusions without fever (cold effusions) present with negative pressures.

On the basis of these statistics we would then state two points of considerable importance: (*1*) The incidence of fluid in pneumothorax therapy is less in cases having negative pressures than in cases having positive pressures; and (*2*) the incidence of tuberculous empyemata and mixed empyemata is materially less in cases having negative pressures than in cases having positive pressures.

The influence of pressures upon fluid formation does not seem to hold water in view of the large incidences of fluids with negative pressures. In addition, we have a large number of cases with positive pressures

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pneumothorax side uppermost and after the refill had been given. By "negative" is meant that the manometric readings during inspiration remained below zero throughout the period of pneumothorax therapy which was studied. By "positive" is meant that the manometric readings were above zero during both inspiration and expiration after the refill had been given for at least one week of the period of pneumothorax therapy which was studied.

without fluids and also a larger number of cases in which positive pressure did not appear until after the appearance of fluid. The only supporting evidence that we have of the theory that positive pressures cause fluid is the small number of cases with positive pressures preceding effusions. This group makes the question controversial. The presence or absence of effusion with positive pressures allows these statistics to be used as desired, but it is our impression that the balance lies in favor of fluids causing pressures rather than pressures causing fluids. This is especially so with the standard method of treatment but conversely with the new method. However, 186 (73 per cent) of the total effusions (253) had negative pressures prior to the occurrence of the effusion and the majority of these fluids were small and not hot.

Study of the statistics bearing upon the relation of the primary effusions to subsequent effusions discloses the following:

1: 190 (75.4 per cent) of the primary effusions (253) did not develop subsequent effusions; 111 (58.4 per cent) of them were cold effusions and 79 (41.6 per cent) of them were hot effusions.

2: 63 (24.6 per cent) of the primary effusions (253) developed subsequent effusions:

a. 17 (27.1 per cent) of the cold effusions (63) developed subsequent cold effusions and 33 (52.5 per cent) of them developed subsequent hot effusions.

b. 7 (11.1 per cent) of the hot effusions (63) developed subsequent cold effusions and 6 (9.5 per cent) of them developed subsequent hot effusions.

The majority of the subsequent fluids occurred in females and, coincidently, the greatest number arose from small fluids without fever (cold effusions) under treatment by the old method. Several years of study with the new method of treatment should prove most helpful in further deduction upon this point.

We have studied our empyemata by the month and year of occurrence in contrast to the months and years that the cases were under observation. We have observed the following:

Number of fluid cases subsequently developing empyema:

1: 54 (14.4 per cent) of the pneumothorax cases (375) developed empyema.

2: 54 (21.3 per cent) of the total number of cases with fluids (253) developed empyema.

3: 71 (28.1 per cent) of the total number of cases with fluids (253) received treatment for three years or more.

4: 15 (21.1 per cent) of these cases (71) developed empyema.

5: 38 (15.0 per cent) of the total number of cases with fluids (253) received treatment for two years or more.

6: 17 (44.7 per cent) of these cases (38) developed empyema.

7: 56 (22.1 per cent) of the total number of cases with fluids (253) received treatment for one year or more.

8: 15 (26.8 per cent) of these cases (56) developed empyema.

9: 46 (18.2 per cent) of the total number of cases with fluids (253) received treatment for six months or more.

10: 5 (10.9 per cent) of these cases (46) developed empyema.

11: 42 (16.6 per cent) of the total number of cases with fluids (253) received treatment for six months or less.

12: 2 (4.8 per cent of these cases (42) developed empyema.

Time of occurrence of empyemata:

1: 2 (3.7 per cent) first month

2: 4 (7.4 per cent) second month

3: 3 (5.6 per cent) third month

4: 2 (3.7 per cent) fourth month

5: 4 (7.4 per cent) fifth month

6: 2 (3.7 per cent) sixth month

7: 15 (27.8 per cent) second half of year

8: 22 (40.7 per cent) after one year

9: 9 (16.6 per cent) three months

10: 17 (31.4 per cent) six months

11: 32 (59.2 per cent) one year

12: 14 (26.0 per cent) of the empyemata became serous, 6 (11.1 per cent) of them had bronchopleural fistula and demonstrable secondary infection and 13 (24.0 per cent) of them had bronchopleural fistula but no demonstrable secondary infection.

Generally speaking, the longer the duration of pneumothorax therapy the greater the incidence of empyemata.

Fifty-four cases of empyemata were observed, representing about 43 per cent of the primary and subsequent hot effusions, 21.3 per cent of the total effusions and 14.4 per cent of the total cases reviewed.

The majority of the empyemata arose from first effusions.

There was a much higher incidence of empyemata among the males than among the females.

The incidence of empyemata with the standard method of treatment

seems too high even though there is a disproportion in number of cases between the standard and new methods.

The final statistics which I wish to present pertain to therapeutic success. By this we merely imply a closure of the cavity on the side of the pneumothorax. The following points were brought out in a review of our data on this subject:

Relation of therapeutic results to type and incidence of pleural effusions and pneumothorax treatment:

A. Therapeutic success:

1: 238 (63.4 per cent) of the operable pneumothorax cases (375) were successful.

2: 238 (68.2 per cent) of the complete pneumothorax cases (349) were successful.

3: 124 (52.1 per cent) of the successful pneumothorax cases (238) had cold effusions, 44 (18.5 per cent) had hot effusions, 168 (70.5 per cent) had effusions and 70 (29.5 per cent) of them had no effusions.

B. Therapeutic failure:

1: 111 (29.7 per cent) of the operable pneumothorax cases (375) were unsuccessful.

2: 111 (31.8 per cent) of the complete pneumothorax cases (349) were unsuccessful.

3: 31 (28.0 per cent) of the unsuccessful pneumothorax cases (111) had cold effusions, 44 (39.6 per cent) had hot effusions, 75 (67.6 per cent) had effusions and 36 (32.4 per cent) of them had no effusions.

C. Incomplete cases:

1: 26 (6.9 per cent) of the operable pneumothorax cases (375) were incomplete.

2: 6 (23.1 per cent) of the incomplete pneumothorax cases (26) had cold effusions, 4 (15.4 per cent) had hot effusions, 10 (38.5 per cent) had effusions and 16 (61.5 per cent) of them had no effusions.

Of the 375 cases, 26 were not observed sufficiently long to determine the effect of pneumothorax.

The greatest amount of success was obtained in patients with the cold effusions (small and large fluids without fever) and the greatest number of failures were found among the hot effusions (large fluids with fever).

In concluding, I might say that seldom have we given more than 500 cc. of air at one sitting and that the usual amount varies between

200 cc. and 350 cc. In children the amounts of air introduced have been proportionate. Every effort has been made to use a minor surgical technique and nothing can be introduced other than air into the pleural cavity as long as our designated procedure is carried out by the staff. The patients on the infirmary and semi-ambulant floors are transported to the pneumotherapy unit or pus treatment rooms, and every effort is made to avoid overexertion and chilling of the patient. The fluoroscopy unit is adjacent to the pneumothorax unit.

I could enumerate all the factors which govern our procedure but suffice it to state we have attempted to consider all which bear upon the aetiology, course and management of fluids. However, not unlike most institutions, we have been only partially successful in reducing the incidence of fluids. We shall continue our investigation of both methods of treatment and hope to offer further light upon the subject in the future. The following conclusions represent the results of our studies to date:

1. Age, sex and color seem to have little aetiological bearing upon the occurrence of pleural fluid in pneumothorax therapy.
2. The season of the year appears to have no influence upon the aetiology of fluid.
3. In females the occurrence of pleural fluid is more frequent in the left side.
4. The more advanced and acute the disease of the lung the greater is the incidence of fluid.
5. There is no one specific cause of effusion in our series. A combination of factors involving physiological, pathological and mechanical considerations were present (4).
6. In cases with negative intrapleural pressures the incidence and quantity of fluid are less, also the incidence of tuberculous and mixed empyemata.
7. The occurrence of fluid is greatest during the first six months of pneumothorax treatment.
8. Approximately two-thirds of the pneumothorax cases developed fluid (67.5 per cent).
9. Unless recognized early, hot effusions often complicate the management of pneumothorax.
10. As long as fluids remain cold the patients do well, but as soon as the fluid becomes hot the patients become ill.

11. The majority of all pleural fluids during pneumotherapy are benign.

12. The majority of cases with positive pressures are associated with hot effusions.

13. The majority of empyemata develop during the first year of treatment.

14. Frequent lavage and the replacement of fluid by air is a wise procedure in the treatment of empyemata.

15. Recurring bacillary effusions require persistent and painstaking treatment.

16. Daily temperature and other pertinent records upon discharged cases with fluid (reporting for out-patient treatment) are advised. A good daily record, such as suggested by Dr. Lawrason Brown, is indicated.

17. The old attitude of leaving fluids alone until signs of air hunger, cardiac symptoms and evidence of general discomfiture appear, has been found too conservative.

18. Aspiration of fluid and the persistent introduction of air are indicated to prevent obliterating pleuritides (reëxpanding lung or pleural symphysis).

Part 2

WILLIAM A. ZAVOD

Fluid occurring during pneumothorax therapy is usually considered a complication. Actually, however, only certain types of fluid can be placed under such a heading, while other fluids are absolutely innocuous, as far as can be determined by our present methods of investigation. Though the various types of fluid are well known to every phthisiologist no clear-cut picture of the various types of effusion can be gained from the literature.

Fluids that occur during the treatment of tuberculosis with pneumothorax can be divided into two main types: "hot" and "cold."

1. To the "hot" fluids belong all those that have an onset with a febrile reaction. They are:

a. Tuberculous effusion
b. Tuberculous empyema
c. Mixed infection pyopneumothorax

2. To the "cold" group belong all those fluids which never cause a febrile reaction at the time of onset or at any time during the persistence of the fluid unless complicated by a "hot" effusion. To these belong:

a. Minimal or fleeting collections of fluid
b. Moderate or fairly large effusions
c. Effusions of reëxpansion

All types of effusion can recur after having disappeared. A "hot" effusion can occur in the presence of a "cold" effusion and the "hot" effusion dominates the picture from then on.

The incidence of all types of effusion in our series of 375 cases was 253 or 67.5 per cent.

I. **Hot Effusions:** *Incidence:* 92 of 253 or 36.4 per cent; 33 of the cold effusions were subsequently complicated by hot effusions, making a total of 125 or 49.4 per cent of 253.

All hot effusions have the following common characteristics:

1: The onset is always acute with a febrile reaction.

2: Mild or severe dyspnoea, headache, nausea, vomiting, loss of appetite, malaise, chills, sweats and pain in the chest may be accompanying symptoms.

3: Fluoroscopic and roentgenographic and physical examinations may fail to show fluid for the first few days following the onset.

4: Tubercle bacilli are found in all cases either on direct smear or on guinea pig inoculation.

5: Inflammatory reaction with thickening of the pleurae always follows the effusion.

6: Loss of weight in varying degrees is associated with all hot effusions.

7: Hot effusions are more common with far advanced lesions (30 per cent) than in moderately advanced lesions (15.1 per cent).

8: Hot effusions are more frequent with acute tuberculous processes (32.1 per cent) than with chronic lesions (19.8 per cent).

The characteristics of the individual types of hot effusions are:

1. *Tuberculous effusions: Incidence:* 71 of 125 or 56.8 per cent. *Clinical course:* The onset is frequently mild and the febrile reaction lasts only a few days to a week. The accompanying symptoms are correspondingly mild. After the febrile reaction subsides, all accompanying symptoms subside with it. The patient regains the lost weight and an improvement in the tuberculous process is frequently seen. The fluid may persist for several months to several years. It may disappear spontaneously or after treatment and it may recur. Moderate thickening of all the structures in the pleural cavity follows. The intrapleural pressure

rises. The rise in pressure is out of proportion to the amount of fluid present in the pleural cavity. The refill intervals have to be lengthened or the amount of air per refill decreased. *Laboratory studies*: Early: The fluid is thin, clear, serous and amber in color. The specific gravity is usually above 1,020. Polymorphonuclear cells predominate and many cells are degenerated. No tubercle bacilli are found on direct smear of the concentrated specimen, but the guinea-pig inoculation is positive for tuberculosis. Late: The fluid becomes cloudy. Lymphocytes predominate. Tubercle bacilli are now found on direct smear. Eventually the tubercle bacilli may disappear from the fluid though they can still be recovered on guinea-pig inoculation.

2. *Tuberculous empyema: Incidence:* 54 of 125 or 43.2 per cent. *Clinical course:* The onset is usually more acute than in the above. The fever persists longer and the loss of weight is greater. The fluid becomes thick within a few days to a few weeks following the onset. The empyema usually persists many months and even several years. The recovery is more gradual and slow. Spontaneous disappearance of the pus is infrequent. In some cases, however, the pus becomes serous fluid again spontaneously or after treatment (14 of 54 or 26 per cent in our series of cases). In others, bronchopleural fistulae may develop (19 of 54 or 35.1 per cent). Some of these become further complicated by mixed infection pyopneumothorax (6 of 19 or 32 per cent). Obliteration of the pleural cavity is a most frequent sequela of this type of fluid. The pathological changes in the pleurae are more pronounced in these cases, with marked thickening of the parietal and visceral pleurae. The intrapleural pressures become positive soon after the onset of the fluid. Absorption of the intrapleural air is markedly slowed. *Laboratory studies*: Early: When examined the first few days following the onset, the fluid differs little from the fluid in a tuberculous effusion. Tubercle bacilli may be found, however, on direct smear. On subsequent examinations the fluid is found to be heavy pus and in many cases contains a pure culture of tubercle bacilli. Late: The pus is fairly thick yellowish-brown or yellow-green in color. Most of the cells are degenerated. Tubercle bacilli may or may not be found on direct smear. Guinea pig inoculation does not always produce progressive tuberculosis in the animals.

3. *Mixed infection pyopneumothorax: Incidence:* 19 of 54 or 35.1 per cent. All these patients had bronchopleural fistulae, but cultures were

positive for secondary organisms in 6 patients only. When this complication occurs in a case of pneumothorax that was free of fluid, it is usually due either to a rupture of the lung from within or to trauma from without, with a resulting temporary or permanent bronchopleural fistula. Mixed infection in most cases arises as a complication of a tuberculous empyema following the development of a bronchopleural fistula. The onset is usually very acute; the course is stormy and the outcome is frequently fatal (12 of 19 or 63 per cent in our series). *Laboratory studies:* The fluid turns into pus within a few days. Tubercle bacilli and other pathogenic organisms are usually found on direct smear and culture. In some cases no secondary organisms can be recovered by the ordinary laboratory methods in spite of proved presence of bronchopleural fistula by clinical methods and postmortem examinations.

II. **Cold Effusions:** *Incidence:* 161 of 253 or 63.6 per cent. In 33 cases a hot effusion developed subsequently, leaving 128 that had a cold effusion only or 50.5 per cent of 253.

These effusions have the following common characteristics:

1: They never cause a rise in temperature unless complicated by a hot effusion.

2: They do not cause loss in weight.

3: They do not produce any symptoms.

4: They are discovered accidentally on fluoroscopic or roentgenographic examinations.

5: They do not cause any change in the intrapleural pressure other than a slight rise due to the addition of fluid in a closed pneumothorax space. The rise is in proportion to the amount of fluid.

6: They cause only slight pleural thickening without evidence of inflammation.

7: They disappear spontaneously without treatment.

8: They recur more often than the hot effusions.

Laboratory studies: Early: The fluid is clear, thin, serous, amber or straw colored. The cytology shows nothing characteristic. No tubercle bacilli are found on direct smear or guinea-pig inoculation. The specific gravity is usually below 1,020. Late: The fluid may become cloudy but never frankly purulent. Tubercle bacilli are absent even when the fluid thickens. Guinea-pig inoculation remains persistently negative.

These findings are contrary to reports in the literature and contrary to the accepted belief that most effusions complicating therapeutic

pneumothorax are tuberculous. (Pinner (3).) Clinical observations and studies of cold fluids by culture and guinea-pig inoculation in our laboratory suggest that most of the cold fluids are probably transudates and nontuberculous. If these fluids are tuberculous, the tubercle bacilli are insufficient in number to grow on culture media or to produce tuberculosis in the experimental animal. The occurrence of fever during the presence of a cold effusion should be interpreted as a superimposed complication of the cold fluid by a hot effusion, if the fever cannot be attributed to the pulmonary lesion proper. The fluid following this complication will show tubercle bacilli either on direct smear, culture or animal inoculation.

Whether these cold effusions are of a very mild tuberculous variety or nontuberculous, the important fact is that the cold effusions are harmless in contradistinction to the hot effusions which constitute a definite clinical and pathogenic entity, profoundly influencing the course of pneumothorax therapy.

The characteristics of the individual types of cold effusion are:

1. *Minimal or fleeting collections of fluid: Incidence:* 123 of 161 or 76.4 per cent. (Of these 21 cases were subsequently complicated by a hot effusion.) These effusions are merely small collections of fluid that fill the sulcus and may be discovered on fluoroscopic examination on the day of the initial pneumothorax treatment. They come and go, thus the term "fleeting." They may occur as many as five or six times in a single patient during the course of pneumothorax therapy. They require no treatment and disappear spontaneously.

2. *Moderate or fairly large effusions: Incidence:* 38 of 161 or 23.6 per cent. (Of these 12 cases were subsequently complicated by a hot effusion.) These may cover the dome of the diaphragm or fill the lower half of the chest. Occasionally, they may fill the entire hemithorax and cause embarrassment by mechanical interference with respiration and circulation. They disappear spontaneously and may recur.

3. *Effusions of reëxpansion:* These occur in all patients treated with pneumothorax when the treatment is discontinued, either because the desired result had been accomplished or the therapy is discontinued because of ineffective collapse. During the time when the lung undergoes reëxpansion fluid appears, probably due to the high negative pres-

sure caused by discrepancy between the rapid absorption of air in the pleural cavity and the slow reëxpansion of the collapsed lung. The amount of fluid may vary from a trace to a fairly large quantity and, when not complicated by a hot effusion, its quantity is in inverse proportion to the capability of the collapsed lung to reëxpand. As the reëxpansion of the lung progresses, the fluid is gradually absorbed. Small amounts, however, may persist for many months and even years and become encapsulated. The fluid is usually pushed from the base upward toward the apex and when the lung is completely reëxpanded a thin layer of fluid and fibrin may still be found over the apex. This fluid does not always cause symphysis between the visceral and the parietal layers of the pleura and in many cases pneumothorax can be reëstablished at some later date unless a hot effusion occurred during the period of reëxpansion.

Part 3

R. MAXWELL FRANKLIN

Details of the technique and results of the method of administration of therapeutic pneumothorax in use at Grasslands Hospital since July, 1935, are described in a preliminary report to which reference has already been made (1). The use of this method was initiated on the theory that any reëxpansion of the diseased lung between refills not only wastes time during the period required to obtain cavity closure or to prove the ineffectiveness of the pneumothorax, but also prevents that evenly progressive type of collapse which would seem to be more nearly correct scientifically.

By the use of daily refills during the active phase of the collapse of tuberculous lesions by therapeutic pneumothorax, we have obtained cavity closure in 74 per cent of those operable pneumothoraces which were under treatment for a period of time sufficient to determine the immediate result of the procedure. In these cases the lesions treated were in the proportion of 35 per cent moderately advanced and 65 per cent far advanced, and the average duration of pneumothorax was longer than in those cases covered by the preliminary report on the frequency of refills. The lesions in the cases described in the preliminary report were in the proportion of 39 per cent moderately advanced and 61 per cent far advanced, and cavity closure was obtained in 66 per cent of

operable pneumothoraces. The average period of time required to close cavity was 10.4 weeks and to prove therapeutic failure 4.8 weeks. Thus it is seen that, though daily refills shorten the phase of active collapse in the majority of cases, general results are improved by devoting longer periods of time to active collapse in certain selected cases before giving up the pneumothorax as a failure. Here it is necessary to use knowledge acquired by long experience with pneumothorax in order to determine just when a pneumothorax should be discontinued as a failure. In cases of therapeutic failure, early reëxpansion of the lung and the early use of supplementary collapse therapy are desirable to prevent delay in cavity closure by other methods and to lessen the opportunity for the development of pleural effusions.

The statistical analysis of the relationships between the use of daily refills and the type-incidence of pleural effusions which has been presented in Part 1 would seem to warrant the conclusion that daily refills not only do not increase the incidence and severity of complicating pleural effusions, but that such refills produce more collapse with less use of positive pressure and do this in a shorter time than can be done with less frequent refills. Whether the use of daily refills decreases the incidence of complicating effusions can be learned only by several years more of study.

Our policy of managing serous effusions is as follows: aspiration of fluid is avoided during the active phase of the pleurisy, unless pressure symptoms require alleviation, and then decompression is achieved by the removal of air instead of fluid. By activity is meant the presence of fever that is due to the pleuritic process, or any tendency of the fluid to increase in amount, with or without fever. A trial aspiration is performed after evidence of activity has disappeared. If there is no febrile reaction or tendency of the fluid to reaccumulate rapidly, aspirations are continued frequently on the premise that persistence of fluid is damaging to the lung and interferes with the management of the pneumothorax. Tuberculous empyemata are aspirated at least twice weekly and aspirations are followed by irrigation of the pleural sac with physiological solution of sodium chloride until the return flow is clear. We have found recently that instillation of an amount of salt solution equal to the amount of pus removed greatly facilitates elimination of the empyema.

Punctures for thoracocentesis are made anterior to the midaxillary line whenever possible in order to decrease the influence of gravity in the development of tuberculous chest-wall abscesses. As a further aid,

seventy per cent alcohol is injected through the pneumothorax needle to clear it before removal and also during removal to inhibit the growth of bacilli that may be left in the puncture wound. The patient is placed in the usual lateral-prone pneumothorax position before the needle is removed, so that fluid left in the pleural sac will not be in contact with the needle and puncture wound as the needle is withdrawn. The patient is instructed not to lie on the pneumothorax side for twenty-four hours following the thoracocentesis.

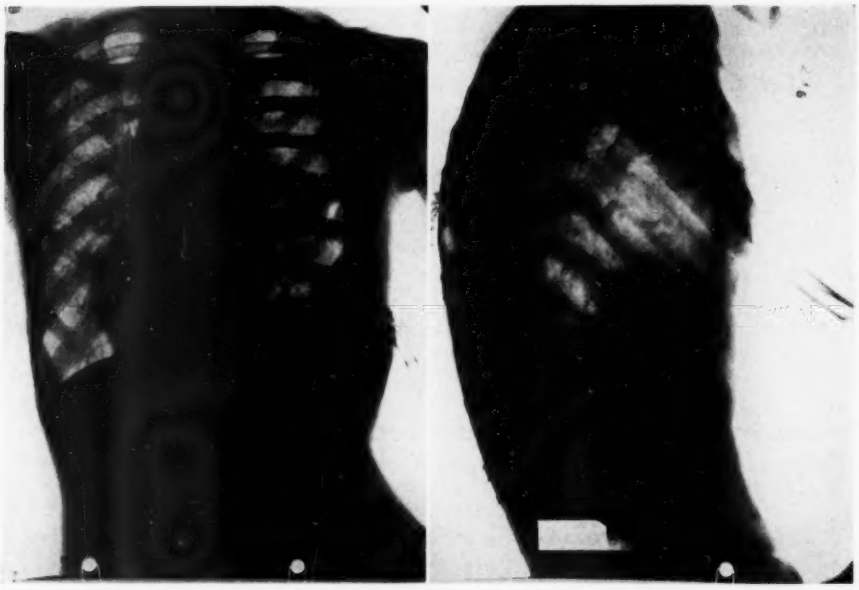

FIG. 1 FIG. 2

FIGS. 1 & 2. Drainage and irrigation tubes *in situ*, left pleural sac

The persistence of free communication between the bronchial tree and the pleural sac is taken as ample indication for the institution of tube drainage of the empyema, regardless of whether or not microörganisms other than tubercle bacilli have been found in the pleural fluid, because of the danger of spreading tuberculous pus throughout the bronchial tree. In certain selected cases of small bronchopleural fistulae, the infection is treated by daily aspirations and azochloramid instillations. The drainage tube is inserted through an intercostal space anteriorly, whenever breast tissue and free pleural space permit, in order to avoid the disagreeable effects of contact of pus with the wound through

the force of gravity. The drainage tube is connected to a siphon and may be left *in situ* indefinitely. A catheter inserted through the same wound is used for continuous or periodic irrigation, whichever is indicated by the position and size of the bronchopleural fistula. (See figures 1 and 2 for roentgenograms revealing tubes *in situ*.) We have found that this method of closed tube drainage of the pleural sac permits us to bring more patients through the acute stage of mixed infection empyemata and thus prepare them for thoracoplasty, if they are otherwise suitable. Its use is cleaner than drainage through a posteriorly located wound, thus being more convenient for the nurse and physician and more agreeable for the patient. A description of the method has been submitted for publication (2).

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NATURE OF PLEURAL EFFUSIONS COMPLICATING ARTIFICIAL PNEUMOTHORAX [1]

EDGAR MAYER AND MARTIN DWORKIN

From tonight's discussion it is apparent that the study of pleural effusions complicating pneumothorax has resulted in a more uniform opinion regarding their incidence, course and treatment. The figures cited by various hospitals handling the same stages of disease are comparable. The treatment of serous effusions varies little; that of tuberculous and of secondarily infected empyemata has been more clearly defined. There still exists, however, a great difference of opinion regarding the aetiology and prevention of effusions. Uncertainty of mode of action of pneumothorax accounts chiefly for this. Recently, Christie's (1) findings have helped to crystallize our concepts.

The factors likely to enhance healing under pulmonary collapse are: (*1*) rest of the collapsed lung, partial or complete; (*2*) relaxation of the lung; (*3*) altered pulmonary blood circulation producing hyperaemia, stasis or relative anaemia; (*4*) altered gaseous exchange of the lung, with resulting anoxaemia and increased carbon dioxide; (*5*) lymph stasis; (*6*) atelectasis and bronchial obstruction; and (*7*) avoidance of aspiration disease in the collapsed lung.

Let us briefly consider the nature of pleural fluids from the standpoint of their aetiology and of preventive therapy.

Pleural effusions complicating pneumothorax are generally of two kinds, transudates and exudates. The former represent disturbances of circulation of fluid in the chest, caused by changes in the mechanics of breathing and the circulatory dynamics that are associated with pneumothorax; the latter represent involvement of the pleura due to direct extension of the pulmonary process. Transudates may of course be transformed at any time into exudates by complicating tuberculous involvement of the pleura during the course of pneumothorax treatment.

[1] Presented at the Clinical Session on Chronic Pulmonary Diseases, Tuberculosis Sanatorium Conference of Metropolitan New York, Cornell University Medical College, New York City, October 7, 1936.

Undoubtedly the great majority of pleural fluids complicating pneumothorax are transudates. Studies in several series of cases show that 70 to 80 per cent do not reach much above the upper level of the costophrenic sinus. Small transient puddles of fluid lasting a few days or more are present in most cases at one time or another. Moderately large pleural effusions complicate about 50 per cent of pneumothoraces.

The circulation of fluid in the organs of the chest is apparently disturbed by pneumothorax. Christie (1) in his recent studies showed that pneumothorax produces a decrease in the distensibility of the lung and a marked rigidity, in all likelihood due to a passive congestion of the organ. According to Cloetta (2), the microscopical picture certainly suggests capillary engorgement. This decreased distensibility of the lung appears to be due rather to passive than active pulmonary congestion, because all evidence shows a decrease in blood volume in the collapsed lung proportionate to the degree of collapse. This rigidity is identical with pulmonary congestion and oedema found in congestive heart failure. With such cardiac decompensation, transudations into the pleural space are not infrequent.

It has been shown by Yamada (3) on several hundred normal soldiers that a small amount of fluid (10 to 15 cc.) is normally present in the pleural cavity, lubricating the gliding pleural surfaces; and is kept there by the continued maintenance of the process of filtration and absorption keeping close pace with one another. Any change in the mechanics of breathing in the chest and in the circulatory dynamics leading either to increased filtration of fluid or decreased absorption from the pleural space will necessarily bring about fluid accumulation in the pleural cavity.

Experimental data available in the literature show that pneumothorax as such need not materially interfere with the above described circulation of fluid in the chest. Shortly after the establishment of most pneumothoraces, a small amount of demonstrable fluid is seen in the costophrenic sinus. This fluid is a limpid serous filtrate containing little fibrin, protein or cells. Its presence may not be detected by the fluoroscope in the hypersthenic patient with flattened diaphragm, and such transient small effusions are often discovered only accidentally in X-ray films. They represent the majority of pneumothorax effusions, appearing slowly and disappearing usually after a few weeks or months. Fever, as a rule, does not herald their formation and they affect the prognosis little, because they do not interfere with pulmonary collapse.

Corper (4) showed that pneumothorax does not materially interfere with pleural absorption in animals. The absorbing power is invested in the parietal pleura (Loeschke (5)) and, since it has been shown that this absorption is aided by the movements of the chest wall and that such movements are in no way interfered with in pneumothorax, there appears no reason why the normal pleural fluid should materially increase in amount during pneumothorax therapy. Brock (6) concluded from experiments that pneumothorax hastens absorption of the pleural fluid. However, in a high percentage of cases, fluid accumulates and indicates a disturbance in circulation. Such disturbances are not necessarily in the nature of the pneumothorax itself, but they appear to be inherent in the individual variations of technique of application and in variations in the functions of the lung. The predisposing influences of menstruation with its production of increased capillary permeability, of fatigue and of seasonal variations of climate are only to be mentioned in passing as possible affecting factors.

In applying pneumothorax, any factor favoring excessive congestion or oedema of the lung can stimulate accumulation of pleural fluid. The chief operating factors are too sudden pulmonary compression and too sudden and excessive fluctuations of pleural pressure upsetting the normal correlation between ventilation and circulation in the lung.

Too sudden pulmonary compression results in the trapping of excessive blood in a lung only partially collapsed in which the reëxpansion of healthy lung between refills is considerable. Most pleural effusions occur in the first six months, as many as 90 per cent, and about 50 per cent of these in the first two months, which represent the period in which the collapse is still recent and incomplete and is most accessible to the effects of sudden or excessive pressure fluctuations.

Undue fluctuations of pleural pressure and their relation to the degree of expansion of the lung are significant. Exercise, though slight, immediately succeeding a pneumothorax refill in the presence of a partially collapsed lung, acting together with a sudden rise of pleural pressure because of warming of intrapleural air, produces undue pulmonary congestion in a lung whose blood volume has been increased by added respiratory activity. Positive intrapleural pressures are not uncommon at such times even though the terminating pressure of the refill has been negative. In studies of Daniel and Papp (7), great fluctuations of pressure from negative at the start of refills to positive at the end accompanied 90 per cent of effusions, while constant negative

intrapleural pressures both at the start and end of refills accompanied only 11 per cent of effusions. Accordingly studies on ambulatory patients have revealed a greater incidence of pleural effusions.

High positive intrapleural pressures favor accumulation of pleural fluid only if applied too abruptly. Slow gradual deflation of the lung, even though ending in high positive pressure, does not favor fluid accumulation and may perhaps prevent it, because there is thus permitted a gradual reduction of blood volume at the same pace and simultaneous with deflation of the lung. Small and frequent refills carefully applied to a partially collapsed lung perhaps as often as once daily (Nicklas (8)) should favor gradual reduction of blood volume simultaneous with deflation of the lung. High negative pressures following the termination of a course of pneumothorax therapy often cause pleural fluids when pulmonary reëxpansion fails to keep pace with the extreme negative pleural pressure.

In incomplete pneumothorax because of adhesions, pleural effusion is of greater incidence because, first, inadequate collapse does not hinder progression of the tuberculous lesion or impede its extension to the pleural layers, and, second, with inadequate deflation the tamponing effect on the flow of circulation which shunts the pulmonary blood volume is absent, the lung remains congested and pleural effusion is more likely.

Pleural exudates as a rule are characterized by their high fibrin and protein and cellular contents. Their appearance is marked with a sudden rise of temperature and with other clinical symptoms of toxaemia. They are the usual forerunners of tuberculous empyemata. Pleural exudates occur more often with exudative tuberculosis treated by pneumothorax than in those not treated. Pleural exudate indicates generalized pleural inflammation. Under pneumothorax, once the infection extends to the pleura, the entire membrane becomes involved. Normally when the pleural layers are still coapted with the force of cohesion as shown by Sir Arthur Keith, particularly over the upper lobes, involvement of the pleura results only in localized organization of exuded fibrin, gluing together the pleural layers. In pneumothorax, separation of coapted pleura generalizes inflammation of the pleura. When pleural layers are not in contact, exudation accompanying the pleural inflammation will form an effusion; thereby pneumothorax tends to increase the incidence of pleural exudate in exudative pulmonary processes. This explains the higher incidence of pleural effusions in pneumothorax over that in patients without pneumothorax. Acute exudative

pulmonary lesions, particularly with cavity formation, are most frequently complicated by pleural exudate in pneumothorax therapy. Rupture of caseous foci in lung adjacent to tense adhesions, strained by high pressures, is not infrequently a source of purulent effusion. Likewise, effusions are more common in pneumothoraces accompanying exudative disease of small extent than in proliferative disease of great extent. Extensive caseous areas collapsed by pneumothorax frequently are associated with exudative pleurisy. Absorption of pleural exudate too often results in formation of adhesions and frequently obliterative pleuritis develops with pulmonary reëxpansion. Perhaps one-third of such cases become abandoned pneumothoraces. Contrarywise, absorption of transudate allows reëstablishment of pneumothorax, even though years have elapsed following reëxpansion of the lung.

Transition from transudate to exudate is a frequent occurrence particularly in cases where the treatment is persisted in, in face of poor collapse and in the presence of rising fluid accumulation. Such effusions, if long continued, are certain to become infected mostly from the tuberculous process in the lungs and rarely by secondary pyogenic invasion.

In *spontaneous pneumothorax*, effusions do not form in the nontuberculous cases, but they regularly do in tuberculous perforations. In the former the lung is deflated completely or at least immediately upon the onset of the attack, and reëxpansion of the lung is gradual. From the completely deflated lung no effusion can be filtered out. Even with artificial pneumothorax, complete pulmonary collapse has remained free of pleural effusion for many years. As the lung gradually reëxpands effusion does not form because absorption and filtration keep simultaneous pace with each other. Here we have the ideal example of the absence of fluctuation in degrees of inflation and deflation of an incompletely collapsed lung. In perforation of a tuberculous lung, however, complete deflation is often not present because of pleural adhesions, and infiltrations and congestions in the diseased lung favor the formation of pleural fluids.

CONCLUSIONS

1. Partial collapse involving excessive fluctuations of intrapulmonary and intrapleural pressure is a paramount factor in the production of pleural effusion complicating pneumothorax.

2. Functional activity of the organ greatly augments the effect of these factors by increasing the circulatory burden in the lungs.

3. Management of pneumothorax under careful avoidance of sudden or excessive pressure fluctuations and utmost restriction of exercise during the period of establishment of effective pneumothorax should prove the most important measure of preventing pleural effusions.

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MASSIVE PLEURAL EFFUSIONS IN ARTIFICIAL PNEUMOTHORAX[1]

Their Influence on the Underlying Pulmonary Tuberculosis

MILTON B. ROSENBLATT

Pleural effusion is the commonest complication of artificial pneumothorax, interfering with the successful outcome of collapse therapy more often than any other complication or accident. Fishberg (1) in his review of the subject states that the beneficial effects noted in a few instances are easily balanced by the vast majority of cases in which extensive and prolonged effusions, even though they remain serous, exert a deleterious effect. It is also stated that while effusions may remain serous for months that such an outcome is exceptional and that sooner or later the fluid becomes purulent. Even if the fluid absorbs there results an obliterative pleuritis which in the process of formation produces a progressive increase in the intrapleural pressure necessitating abandonment of the pneumothorax. It is further alleged that when the fluid is completely absorbed the parenchyma is converted into a mass of fibrous tissue in which large cavities and dilated bronchi may remain. There apparently is a general agreement that fluid when it occurs in the course of artificial pneumothorax should be aspirated as often as necessary and replaced with air.

With observations which suggest that the presence of some pleural fluid occurs in every case of pneumothorax, it can readily be seen that the complication is of considerable importance. Fortunately, in the vast majority of instances, the fluid is insignificant in amount and soon absorbs with little or no interference with the collapse-therapy program. The adhesions which result from the absorption of these transient effusions may be undesirable from a theoretical standpoint but rarely do they offer any serious interference either with the pneumothorax or subsequent collapse measures. It is the massive effusions which create the problems of therapy. The high positive intrapleural pressures contraindicate further insufflations so that if the pneumothorax is to be continued the fluid must be removed.

[1] From the Tuberculosis Division of the Montefiore Hospital, New York City.

From time to time, however, there have been observed isolated instances in which the fluid was allowed to remain undisturbed except for diagnostic aspirations and there resulted a decidedly beneficial effect on the course of the pulmonary disease. Owing to the general tendency to withdraw fluid the opportunities for observation and follow-up of these cases have been limited. We, therefore, decided to review a group of these cases over a period of many years to determine the ultimate effect of massive effusions. It is to be emphasized at the outset that this discussion is limited to serous effusions occupying at least one-half of the pleural cavity.

Between the years 1920 and 1935 there were but nine cases at the hospital in which a massive effusion occurring in the course of artificial pneumothorax was voluntarily permitted to remain intact with subsequent abandonment of the pneumothorax. Because of the small number, the cases are presented individually.

CASE REPORTS

1: M. S., a peddler, 31 years of age, was admitted on January 26, 1923, with a history of pulmonary tuberculosis of ten weeks' duration. Examination showed a fibrocaseous involvement of the entire left lung with a large cavity in the upper lobe. His right lung was normal. The temperature ranged between 99° and 100°F., the sputum was positive, and his weight was 100 lbs. Pneumothorax was induced on March 2, 1923. Fluid was first noticed on April 26, 1923, but refills were continued at irregular intervals until March 17, 1925, when pneumothorax was discontinued. The fluid continued to increase and in November, 1925, had reached the fourth rib in the midaxillary line. Aspiration showed it to be serous and it did not contain tubercle bacilli on smears and cultures. The fluid level remained practically stationary for several months and then began gradually to diminish. Roentgen examination on August 18, 1926, showed definite absorption. The patient was discharged on October 28, 1929, with sputum negative on smear and concentration, afebrile, and weight of 132 lbs., and has since been under observation in the Out-Patient Department. He is well and able to work. His last film taken on April 8, 1936, eleven years after discontinuation of pneumothorax, showed scattered fibrotic infiltrations throughout the left lung with pleural thickening at the base. The absorption of fluid is complete and the right side is still normal. This patient was also a moderately severe diabetic.

2: M. G., a machine operator, 21 years of age, was admitted on April 11, 1925. His illness began with productive cough two months previously. Examination showed an exudative infiltration of the right upper lobe. The tempera-

ture ranged between 100° and 104°F. The sputum was positive and the admission weight was 180 lbs. Pneumothorax was induced on the right side on April 20, 1925, and was continued for four months until August 21. The temperature declined after induction of pneumothorax but continued to range between 99° and 101°F. Fluid was first noticed in August and by the end of September had reached the level of the fourth rib in the midaxillary line. Aspiration showed it to be serous and free of tubercle bacilli (smear and culture). At the onset of the effusion there was a febrile reaction with the temperature rising to 103°F. However, the fever declined rapidly and two weeks later the temperature was normal. The patient's condition improved steadily and he was discharged on October 19, 1925, with negative sputum (smear and concentration) and afebrile. The discharge weight was not recorded. Examination one year later on September 8, 1926, in the Out-Patient Department showed that the fluid had absorbed leaving a thickened pleura. His general condition was excellent and he weighed 205 lbs. He has been well and able to work ever since. At present he is working full time. His last X-ray film in June, 1936, eleven years after discontinuation of pneumothorax, showed only residual fibrosis.

3: D. G., a 30 year old tailor, was admitted on June 19, 1931. His illness was of three months' duration and characterized by frequent haemoptyses. Examination showed a fibrocaseous infiltration of the entire right lung with a large cavity in the upper lobe. The sputum was positive, the temperature ranged between 99° and 100°F., and his weight was 141 lbs. Pneumothorax was induced on the right side on June 26, 1931, and was maintained for two months until August 31, 1931, at which time there was a 70 per cent collapse with adhesions of the middle and lower lobes. Fluid was first noticed on August 14, 1931, and gradually increased until March, 1932, when it reached the apex. Absorption began shortly after this, and by February, 1933, the fluid had descended to the fifth rib in the midaxillary line. On the first aspiration in August, 1931, the fluid was serous and contained tubercle bacilli. The patient was aspirated on seven different occasions for diagnostic purposes and eventually the fluid became turbid. However, it never contained more than 3,000 white blood cells per cubic millimetre and showed no organisms other than tubercle bacilli. After the onset of the effusion the temperature rose to 102°F. for ten days and then declined to between 99° and 100°F. The general condition after the subsidence of the febrile reaction was greatly improved and this improvement continued during the succeeding months. The patient was transferred to the Country Sanatorium on February 20, 1933. He was afebrile and weighed 151 lbs., but the sputum was still positive. In May, 1934, the sputum became negative (smear and concentration) and the fluid had practically absorbed. The patient was discharged to the Altro Work Shops in

February, 1935, and worked full time as an operator. His last X-ray film on December 31, 1935, almost five years after discontinuation of pneumothorax, showed fibrotic infiltration of the right upper lobe with pleural thickening and retraction of the trachea to the right. The sputum has been persistently negative. In July, 1936, he was discharged from the Altro Work Shops to resume work in normal industry.

4: B. S., a 24 year old cab driver, was admitted on January 7, 1932, complaining of productive cough of two months' duration. Examination showed an exudative infiltration of the left lung with a cavity in the upper lobe. The right side was normal (figure 1). The sputum was positive, the temperature ranged between 99° and 102°F., and his weight was 149 lbs. Pneumothorax was induced on January 12, 1932, and continued for four months until May 4, 1932, at which time the lung was collapsed 80 per cent. Fluid was first observed in March, 1932, and increased rapidly until May when it reached the level of the third rib in the midaxillary line (figure 2). The pleural cavity

FIG. 1. Case 4. January 9, 1932. Exudative infiltration of the left lung with a cavity in the upper lobe. Right side is normal.

FIG. 2. Case 4. June 4, 1932. Hydropneumothorax with massive effusion displacing heart and mediastinum to the right. The left lung is completely collapsed. Right side is normal.

FIG. 3. Case 4. November 11, 1935. The effusion is completely absorbed and the left lung is reëxpanded. There is slight fibrosis scattered throughout the left lung and the pleura is thickened. The heart is deviated slightly to the left. The right side remains normal.

was aspirated twice and on both occasions the fluid was serous and contained tubercle bacilli but no other organisms. The patient's entire course of illness was one of rapid improvement. He was transferred to the Country Sanatorium on August 4, 1932, with negative sputum (smear and concentration), weight of 166 lbs., and afebrile. However, he left there of his own accord on September 2, 1932. He is under observation at present in the Out-Patient Department. He is well and able to work full time. His last X-ray film on November 11, 1935, showed all the fluid absorbed leaving a thickened pleura. There is slight fibrosis scattered throughout the left lung. The right side is still normal. There is slight retraction to the left (figure 3).

5: C. V., a 45 year old housewife, was admitted on May 5, 1934. Her illness began in 1929 with a sudden haemoptysis. In May, 1933, pneumothorax was induced by a private physician and maintained for seven months without successfully closing a large cavity in the right upper lobe. In January, 1934, the patient was admitted to Bellevue Hospital where she stayed for two months with continuation of the pneumothorax. In March, 1934, she was

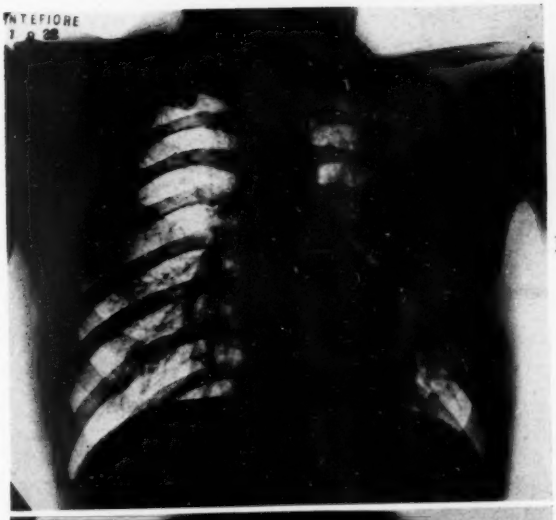

FIG. 1

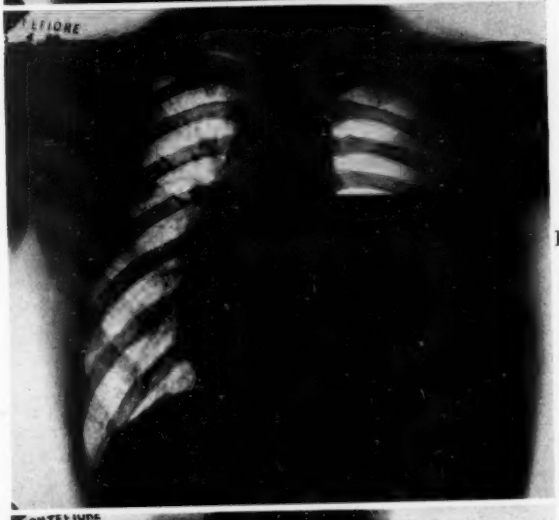

FIG. 2

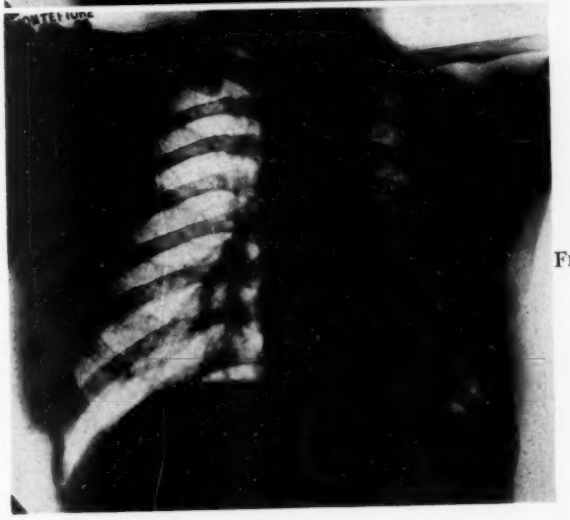

FIG. 3

FIGS. 1–3

admitted to the Willard Parker Hospital. Roentgen examination at that time showed a thick-walled cavity occupying almost the entire right upper lobe and a nodular dissemination in the midhilar region of the left lung. The right lung was collapsed about 50 per cent by the pneumothorax, and there were two adhesions extending from the right upper and lower lobes, respectively. Fluid was noted at the right base in April, 1934, but pneumothorax was continued until May, when increasing positive pressures prevented further refills. When she was admitted to Willard Parker Hospital the temperature ranged between 99° and 102°F., but after the onset of the effusion it subsided rapidly. The patient was transferred to Montefiore Hospital on May 5, 1934. She was afebrile, weighed 172 lbs., but the sputum was still positive. There was a moderate effusion with the right lower lobe completely collapsed and the upper and middle lobe partially collapsed. Aspiration of the fluid showed it to be slightly turbid and containing no tubercle bacilli or other microörganisms on smear and culture. A pneumothorax refill was given on one occasion shortly after admission. The fluid level continued to rise and by December 18, 1934, had reached the apex. In June, 1934, thirteen months after pneumothorax had been instituted and two months after the occurrence of the effusion the sputum became negative (smear and concentration). It remained negative on 15 subsequent examinations. On December 20, 1934, 1,400 cc. of the fluid was removed. It was serous, contained 220 white cells per c.mm. and showed no microörganisms. Roentgen examinations in February and April, 1935, showed the cavity distinctly smaller. The patient was discharged on May 9, 1935, with negative sputum, afebrile, and weighing 200 lbs. She is ambulant and able to do her housework. Her last X-ray film in August, 1936, showed disappearance of the cavity and dense fibrosis in the right upper lobe. The fluid had absorbed leaving a thickened pleura. There was slight retraction of the mediastinum. The sputum was negative.

6: L. S., a 46 year old insurance agent, was admitted on August 13, 1931 with a history of pulmonary tuberculosis of one year's duration. He had a pneumonic consolidation of the left lung with a moderate sized cavity in the upper lobe. There was also a fibrotic infiltration in the right upper lobe. The sputum was positive and the temperature ranged between 99° and 102°F. His weight was 106 lbs. The patient was observed for two months but no changes were noted. Pneumothorax was then induced on the left side on October 14, 1931. Fluid was noted the following day. Pneumothorax was continued for two and a half months until December 31, 1931, at which time there was an 80 per cent collapse of the left lung with a broad axillary adhesion. The fluid level rose gradually and at the end of March, 1932, had reached the apex. The effusion was aspirated on five occasions. It was serous each time and contained no tubercle bacilli or other organisms on smear and culture.

By January, 1932, the temperature ranged between 99° and 100°F., and after February, it was normal. At this time the patient began to gain weight. His general condition improved greatly. The right side remained unchanged. The patient was discharged on September 4, 1932. His sputum was negative on smear and concentration; he was afebrile; and his weight was 132 lbs. He has remained well since his discharge but, because of a strong psychoneurotic element, has been unable to resume his former occupation. He entered the Metropolitan Hospital on May 26, 1936, purely for custodial care with no pulmonary symptoms. His last roentgen examination on March 9, 1937, showed the left lung to be fibrotic and retracted with no evidence of fluid. The right lung was normal. All sputum examinations, including gastric lavage, were negative.

7: E. A., an 18 year old girl, a stenographer, was admitted on November 8, 1923. She had been ill for three months prior to admission. She had a fibrocaseous tuberculosis of the entire left lung with two large cavities in the upper lobe. There was also a fibrotic lesion in the right lower lobe. The sputum was positive and the temperature ranged between 99° and 102°F. The weight was 117 lbs. Pneumothorax was induced on the left side on November 13, 1923, and fluid was first noticed on December 3, 1923. The temperature declined considerably after the introduction of air and continued to drop after the appearance of the fluid. The fluid was aspirated and replaced with air on ten different occasions between December, 1923, and May, 1924. At the onset it was serous but on the last two aspirations it was turbid. Smears and cultures revealed no tubercle bacilli. There was no further aspirations after May, 1924, and the fluid was allowed to remain intact. In September, 1924, the fluid level reached the third rib in the midaxillary line and in November extended to the apex. Shortly afterward the effusion began to absorb. The general condition at this time was one of continued improvement. The patient was discharged on January 5, 1925, with the fluid level down to the sixth rib in the axillary line. The left lung was still well collapsed and the right side was unchanged. She was afebrile, sputum was negative, and her weight was 157 lbs. (a gain of 40 lbs. since admission). Examination in the Out-Patient Department, one year later, in January, 1926, showed the general condition to be unchanged. Roentgen examination at that time showed additional absorption of the fluid but no other change. No further follow-up was obtainable.

8: S. G., a 45 year old housewife, was admitted on August 21, 1923 with a history of pulmonary tuberculosis of three years' duration. She had several large cavities in the left upper lobe associated with a thickened pleura from apex to base. The right side was normal. Sputum was positive, temperature

ranged between 99° and 100°F., and the admission weight was 150 lbs. No special therapy was given for three months during which time the condition remained essentially unchanged. In November, 1923, the patient became acutely ill and roentgen examination showed an exudative infiltration in the right upper lobe. At this time it was decided to give pneumothorax which was induced on November 18, 1923, and maintained for nine months until August 9, 1924. The first appearance of the fluid was not noted, but by December 1, 1924, it had reached the level of the fifth rib in the midaxillary line. Aspiration showed it to be serous. No bacteriological study is recorded. The course of the patient after the spread to the right side in November, 1923, showed no improvement despite the pneumothorax and the effusion. She continued febrile and the sputum remained positive. On December 7, 1924, she left the hospital of her own accord. Although there had been no additional progression of the disease on either side her general condition was poor and she weighed 28 lbs. less than on admission. No follow-up is obtainable.

9: A. R., a 23 year old girl, a cashier, was admitted on November 1, 1927 with a history of productive cough of seven months' duration. Examination showed a fibrocaseous involvement of the right upper lobe with numerous small cavities and scattered fibrotic infiltrations throughout the middle and lower lobes. The left side was normal. The temperature ranged between 99° and 101°F., and her weight was 110 lbs. There was no sputum. Pneumothorax was induced on November 20, 1927, and maintained for three months until February 16, 1928. The onset of fluid was not recorded, but by February it had reached the level of the fifth rib in the midaxillary line, and by May, 1928, it reached the apex. There were no diagnostic aspirations. The course continued febrile until February, after which the temperature rapidly declined. Her general condition improved greatly. She was discharged on June 2, 1928, weighing 130 lbs. (a gain of 20 lbs.), and afebrile. There was no sputum at any time. The patient was well for five years after discharge and during the years of 1932 and 1933 worked for twelve hours daily. In the latter part of 1933 she suffered an exacerbation of her pulmonary disease and examination showed involvement of the contralateral side and positive sputum. She died on August 10, 1934, in the St. Joseph's Hospital of progression of her pulmonary tuberculosis.

COMMENT

In summarizing the results two facts stand out very prominently. The first is that none of the unfavorable complications materialized, and the second is that the ultimate results were far better in this group than in the entire group of all pneumothorax cases of which they were but a small part.

One of the important objections to permitting pleural effusions to remain intact is the danger of their becoming purulent. Of the seven cases in which the pleural fluid was aspirated there were no instances of empyema. However, in two of them the fluid was turbid. These were the patients with the greatest number of aspirations. The second major objection was that the fluid, if it did not become purulent, would remain unabsorbed for a long period and embarrass the patient's condition in many ways. The patients whom we were able to follow up after discharge showed complete absorption of the fluid with only residual thickening of the pleura. Retraction of the trachea or mediastinum was slight and did not cause respiratory or cardiac difficulties. Following the absorption of the fluid no open cavities remained. On the contrary, the pulmonary disease seemed healed in a most effective manner with only scattered fibrotic infiltrations as scars of the former caseating lesions. Another objection is that the presence of the fluid will result in the formation of adhesions which will prevent the continuation of pneumothorax at a later date if it were necessary. Whether it was a mechanical or a biological action cannot be ascertained, but certainly the ultimate results obtained seemed to be quite final and the question of reëstablishing pneumothorax did not arise.

Furthermore, the period of active therapy was materially shortened. Penumothorax refills are usually maintained for two years of treatment and often as long as five years before the physician feels that it is safe to permit reëxpansion of the lung. Many patients are continued for even longer periods during which times, disregarding the possibility of accidents, the patient is still considered an invalid. While the mere presence of a massive effusion did not abruptly alter the patient's clinical condition the subsequent clinical course was invariably one of improvement. Case M. S. had had pneumothorax for two years before the effusion filled the pleural cavity. Following this there was no need for further treatment. Cases M. G., B. S. and C. V. had pneumothorax for 13 months. Case S. G. had refills for nine months and case A. R. had pneumothorax for three months. Cases L. S. and D. G. had refills for only two months. The average duration of active therapy in these patients was far less than for pneumothorax cases in general and the results are far more encouraging. If we do not consider the patient who had bilateral disease at the time pneumothorax was induced, all of these patients were discharged as improved with negative sputum. Six of these patients have been followed up to the present, from one

and a half to ten years after discharge. All are alive, well, working or able to work. This is in marked contrast to the statistics of Rubin (2) for all of our cases of pneumothorax, followed two to fifteen years. Forty-three per cent of the patients were dead and only thirteen per cent were able to work.

The general policy to remove large pleural effusions and replace them with air has been arrived at after many years of observation and for apparently valid reasons. The removal of fluid diminishes the formation of adhesions, prevents interruption of collapse therapy, and, in general, permits the control of the case to rest with the physician rather than with the natural processes of fibrosis and retraction. Dundee (3), in a discussion of pneumothorax, is definitely of the opinion that fluid should be aspirated and replaced with air as often as necessary. At the Tuberculosis Sanatorium Conference of Metropolitan New York, held in October, 1936, this was also the consensus. There are, however, some important exceptions. Rist and Veber (4), for example, believe that in the majority of instances pleurisy with effusion is an aid to recovery rather than a hindrance. In a large series of cases they often noted that following the onset of effusions patients who had showed little progress under collapse therapy began to improve rapidly. They found that of 465 patients discharged after one and a half to eight months of pneumothorax treatment 262 still had positive sputum after leaving the hospital. Seventeen per cent of these had had effusions. Of the 203 whose sputum had become negative, 32 per cent had had effusions. However, no differentiation was made as to the extent of the effusion which is the main issue under discussion here. Inasmuch as most cases of artificial pneumothorax have effusions at some time it is rather difficult to attribute a favorable prognostic significance to the mere presence of fluid. As a matter of fact in Rubin's (2) statistics the incidence of pleural effusion was just as high in the patients who had died as in those who had survived.

I am convinced by the results obtained in these patients that the prognosis of the patient who has developed a massive effusion in the course of artificial pneumothorax is far better ultimately than that of the patient in whom collapse therapy is continued by removal of the fluid. I am referring essentially to those cases of dominantly unilateral disease; neither pneumothorax nor fluid can be expected to be of much value where the contralateral side is seriously affected. The condition on discharge of the patients in this series, the short duration of treat-

ment, and the follow-up mortality are important arguments toward establishing a uniform policy of handling such cases. Where the amount of fluid is insufficient to interfere appreciably with pneumothorax refills they should be continued with no regard to the presence of the fluid. However, when the effusion has reached massive proportions so that it is impossible to continue further insufflations, the pneumothorax should be completely abandoned and the fate of the disease left with the effusion. I believe that the facts presented above warrant this conclusion.

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A FIVE-YEAR REVIEW OF TUBERCULOSIS IN COLLEGE STUDENTS[1]

LEE H. FERGUSON

The recognition of tuberculosis as a serious menace to the health of American college students has been slow in developing and is of comparatively recent origin. This, however, has been true of all college health work. As the two are inseparable and a tuberculosis program can be successful only when it rests on a broad foundation of general health principles, it might be well for us to trace briefly the development of college health work. There are some interesting historical data on this subject.

Physical education *en masse* was introduced into this country from Germany and Scandinavia in 1825 and had a very rapid development. At first it was assumed that an exercise program was all that was necessary for health. The Boston Medical Intelligencer of September 25, 1827, in commenting on the exercise program at Williams, said, "We may hope that our students will no longer, as in former years, leave college with emaciated frames and pallid countenances through want of proper exercise."

For about thirty-five years the health programs in our colleges centered in the gymnasium and were considered adequate. The first suggestion that more was needed came from President William A. Stearns, of Amherst, in 1856. He said, "The breaking down of the health of the students, especially in the spring of the year, which is exceedingly common, involving the necessity of leaving college in many instances, and crippling the energies and destroying the prospects of not a few who remain, is in my opinion wholly unnecessary if proper measures could be taken to prevent it."

Later in 1859, due to the death of two students in the senior class, one of whom died of tuberculosis, the trustees of Amherst authorized the construction of a building which was the nucleus and beginning of a department known as Physical Education and Hygiene. Vassar devel-

[1] Presented at the Fourth Annual College Hygiene Luncheon, at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

oped a similar department in 1865. To Doctor Edward Hitchcock, who was in charge of the department at Amherst, therefore, belongs the distinction of being the first medical man to inaugurate a complete health program in an American college.

Doctor Hitchcock's program, as outlined by Doctor Joseph Raycroft of Princeton, was as follows:

1: Medical examination of each student
2: Instruction in the hygienic way of life
3: Regular prescribed physical exercise throughout the four-year course
4: Treatment of the sick
5: Annual report of the workings of the plan, and particularly the kind and number of sicknesses from which the students suffered

The above certainly is modern in every way and the wonder is that anything so vital was forty years in developing in our institutions of higher education. In passing I might add that Doctor Hitchcock's favorite prescription for students who consulted him is reported to have been "Trust in God and keep your bowels open." Rather good advice even for to-day.

Prior to 1900 college health work, as far as the medical profession was concerned, consisted chiefly in the operation of infirmaries for sick students. Between 1890 and 1900, due to the increased interest in intercollegiate athletics, doctors commenced to take some part in athletic training and the care of athletic injuries. It was not, however, until after 1900 that physicians became interested in the whole problem of student health.

Between 1900 and 1920, when the American Student Health Association was organized, health work developed very rapidly, but, in general, suitable standards were lacking and facilities inadequate. During this period, however, the doctor was assuming more and more responsibility for the solution of all the health problems relating to student life. His status in the educational plan changed from that of one who cared only for the sick to that of a health administrator and coördinator. Of course he still cared for the sick student; but he also became concerned about the so called well student, his adjustment to college life, his mental, emotional, and physical problems, his environment, and also health teaching. In this new program the early discovery of serious conditions such as tuberculosis was bound eventually to receive due consideration.

Now, if we turn to the problem of tuberculosis in college students we are struck by the almost palsied slowness with which adequate programs were developed. By 1920, when the American Student Health Association was organized, tuberculosis was taking a terrible toll in our American colleges. Students were dropping out with this disease, were being sent to sanatoria, and were dying from it; but still we were content to wait for the disease to declare itself before anything was done. This state of affairs existed for years, and it was not until recently that our attitude has changed.

The lack of interest is very clearly shown by the fact that between 1920 and 1929, although yearly meetings were held, only one paper on tuberculosis was read before the American Student Health Association. This was by Doctor J. A. Myers and Doctor W. B. Shepard, in 1925, on their experience at Minnesota. The next paper on the subject was one given by me at the tenth annual meeting of the Association in New York, December, 1929, in which it was proposed that a five-year study of the whole problem be made by the Association. This seemed like an idle dream at the time, but through the coöperation of the National Tuberculosis Association it has been at least partially realized and we now have a vast amount of data on this subject. We are reporting to-day on the results of our first five-year plan.

I have been making a survey of some of the larger universities to find out the exact dates of the development of their tuberculosis work. Doctor J. A. Myers, of Minnesota, who was a pioneer in this field and probably has made the greatest single contribution to it, advises that their chest clinic was started in 1920. So far as I know this was the first chest clinic established in the United States in connection with a college or university Health Service. For the first eight years the Minnesota clinic took only the cases that were sent to them with suspicious signs or symptoms and no special effort was made to find all the tuberculosis in the entering classes. In 1928 tuberculin testing of entering students, with X-raying of some of the positive reactors, was started and this probably represented the greatest single step which has been taken in the solution of the tuberculosis problem in college students. It was not, however, until three years later, in 1931, that all the positive reactors in the entering classes were X-rayed and a really complete tuberculosis program was put in operation at the University of Minnesota.

Equally interesting is the development of tuberculosis work at Yale

under the direction of Doctor W. B. Soper. Recently Doctor Soper has written me as follows:

About two years after coming to New Haven in 1926 from Saranac Lake, I received a letter from a Divinity student who had been at Saranac Lake and whom I knew while there. My Divinity student remarked upon the number of students from the various universities whom he had seen at Saranac Lake. He remarked also on his own observation of how much the Saranac Lake physicians depended upon X-ray films. He offered a suggestion that I should work up at Yale University some plan for taking X-ray films of entering students, and stated in his letter that he was also writing to friends at Harvard and at Princeton along the same line. I showed the letter to Dean Winternitz of the Medical School and to Doctor Greenway in charge of the University Health at that time. They both agreed that the idea was probably sound, but that its execution would have to be put off until the new Department of Health Building would be ready. . . .

In 1930 we began with stereo films of all entering students in all departments, some 1600 of them. In 1931–32, in order to economize, we screened through tuberculin and took single films of the positive reactors. In 1932–33 and in 1933–34 we went back to single films of all students without using tuberculin. I do not recall just why we made this change away from the tuberculin test. In 1935–36 we screened through P.P.D. and took single films of positive reactors. In 1936–37 we followed the same procedure. During the past four years we have taken films of both the entering students of the Nursing School and students entering the School of Medicine; not only at the beginning, but also during the spring before graduation.

These pioneer experiences with tuberculosis at Minnesota and Yale are now being repeated at numerous institutions all over the country. They represent a complete change in our attitude on the problem, from one of waiting for the disease to declare itself, which nearly always meant moderately or far advanced tuberculosis, to one of going out to find the disease in its early state before symptoms and signs have developed, when it can be easily cured and its spread prevented. We have now at our disposal in the tuberculin test and X-ray all that is needed for this procedure.

It is clear from the above that somewhere between 1928 and 1931 the general problem of tuberculosis in college students was commencing to receive serious attention and programs were being considered at various institutions, based on tuberculin testing and X-rays. Men like Doctors Myers, McPhedran, Chadwick, and Soper were already at work in the

field and it was not long until the National Tuberculosis Association took an active interest in the problem.

The first tangible result of the changed attitude and new interest came from the report of the Tuberculosis Committee of the First National Conference on College Hygiene at Syracuse, May 5 to 9, 1931. This report recommended a program for tuberculosis including tuberculin testing and X-ray examination and suggested again a five-year study of the problem. At this conference practically no statistics were available on tuberculosis in college students and there was only casual interest in the problem.

Five years later at the Second National Conference on College Hygiene in Washington, D. C., December 28 to 31, 1936, a most noticeable change was evident. The interest was great, reports and statistics were presented on all phases of the subject, and a most comprehensive plan was adopted for the elimination of tuberculosis as a serious menace to student health.

There were two direct results of the Syracuse Conference. One of these was the appointment of a Tuberculosis Committee of the American Student Health Association by the President, Doctor Warren E. Forsythe, consisting of Doctor Lee H. Ferguson of Western Reserve University, Doctor J. A. Myers of Minnesota, and Doctor C. E. Shepard of Stanford. The purpose of this Committee, as stated in its first annual report made at the Twelfth Annual Meeting of the Association, December 29 to 30, 1931, was "to direct the work in a uniform way, and to coöperate with the National Tuberculosis Association in the collection, analysis, and presentation of data, in the working out of methods, and in the solution of other problems which may come up." Eventually Doctor H. D. Lees of Pennsylvania and Doctor R. H. Stiehm of Wisconsin were added to the Committee, and an advisory group of five members was formed.[2] The latter has been most helpful.

A second result of the Syracuse Conference was the calling, at the suggestion of Doctor H. E. Kleinschmidt and Doctor Kendall Emerson of the National Tuberculosis Association, of a preliminary conference in Cleveland on July 14 and 15, 1931, to consider the whole problem of tuberculosis in college students and to work out a suitable program for

[2] These members were Dr. H. E. Kleinschmidt, National Tuberculosis Association; Dr. W. B. Soper, Yale University; Dr. F. Maurice McPhedran, Henry Phipps Institute; Dr. Henry D. Chadwick, Commissioner of Health, State of Massachusetts; and Dr. Esmond R. Long, Henry Phipps Institute.

its solution. This conference was attended by Doctors Kleinschmidt, Ferguson, Myers, Soper, McPhedran, Chadwick and Forsythe. Afterward in a letter Doctor Myers said, "I do not believe I have ever attended a more stimulating and inspiring meeting, and one which promises so much hope in tuberculosis control among the teen age girls and boys." This opinion, I am sure, was shared in by all those who attended the conference and it probably will be remembered as one of the many significant milestones in the long journey toward the eradication of tuberculosis.

It was hoped at the time of the Cleveland Conference to get money from a foundation for a survey but this proved to be impossible on account of the depression. The work, however, went forward under the general direction of the Tuberculosis Committee of the American Student Health Association, and in its Second Annual Report made in December, 1932, a complete "Program for Tuberculosis in College Students" was submitted.

The nature of this report makes it impossible to list all the results which have been achieved in the last five years. I will, however, try to give the most important ones. The first is the actual increase in the number of institutions having active tuberculosis programs. In 1931, only a few schools had such programs. Among the pioneers were Minnesota (1928), Yale (1930), Michigan (1930), Pennsylvania (1931), Western Reserve (1928), and Vassar (1931). In all, there probably were not more than ten institutions with active programs. At the present time, according to the reports which have come in, I should say that tuberculosis surveys have been made at 200 or more institutions, and the list is increasing each year. Of course, many of these institutions do not have well developed health services so their programs are not adequate, but at least the work has been started. From the recent survey of American colleges by the American Youth Commission, completed in 1936–37, Doctor C. E. Shepard reports that 50 colleges have definite tuberculosis programs and 40 of these are tuberculin testing their entering students.

The organization of the sectional groups of the American Student Health Association has been of great assistance in promoting tuberculosis work. In 1931, Ohio was the only section organized. Now there are twelve or fourteen of these local associations, due largely to the patient effort of Doctor D. F. Smiley of Cornell. In Indiana, Pennsylvania, Texas, Washington and Idaho, the State Tuberculosis Associa-

tions have been most helpful in getting these local organizations started. Mention should also be made of the fine assistance which the State Tuberculosis Associations have given in conducting surveys and promoting tuberculosis work at the various institutions.

Another change which has taken place in the last five years has been in the number of papers given on tuberculosis in college students at the meetings of the American Student Health Association and its local sections. This has increased steadily until it has become general practice to have one paper each year on this subject. In addition, papers have also been given at general medical meetings and at the meetings of the National Tuberculosis Association. No doubt these have helped greatly to stimulate interest in the subject, not only among the college groups, but also in the general medical profession.

Perhaps the most notable change has been in relation to tuberculin testing. As late as 1929 a review of the literature led to the conclusion that the tuberculin test had little diagnostic value in adults on account of the high percentage of positives. This was the general view held and the only solution suggested was to X-ray everybody. Starting in 1931, however, we began to realize that in our college groups, at least 50 per cent did not react to tuberculin, and more recently the average percentage of positives has dropped to thirty. Doctor Soper's figures at Yale in 1931–32 showed 62 per cent positive and only 48.4 per cent in 1935–36. It seems probable therefore that the actual incidence of tuberculous infection, as shown by the tuberculin test, is slowly decreasing.

Not only have we come in recent years to depend on tuberculin testing as a screen, but the test itself has become more dependable due to the development of standardized P.P.D. by Doctors Long and Seibert in 1934. This preparation is extensively used in college work at present, and as soon as the price can be reduced further, its use should extend very rapidly. The use of a standardized preparation will permit a more accurate comparison of statistics from various colleges and will also give us a means of measuring the actual extent of tuberculous infection in the college group.

The use of X-ray films and fluoroscope for diagnostic work in tuberculosis has also been greatly extended in the last few years. It is hard for us to realize how limited their use was as late as 1928. If a person became sick, he was X-rayed, but the idea of X-raying large groups was just emerging. X-ray films were expensive, and it is only recently that

the price has been reduced sufficiently to permit their general use. There is still need, however, in many places for a further reduction in cost and for more general recognition of the basic principle that an X-ray or fluoroscopic examination of the chest should be a part of every complete physical examination.

Too much emphasis cannot be placed on the importance of this changed attitude in regard to tuberculin testing and X-raying of students. By these means we can practically make a complete tuberculosis inventory of the individual and the group. We can discover unknown sources of infection in the home or on the campus, can protect the student better while he is in college, and can send him out with knowledge of tuberculosis which should fortify him against the dangers of this disease. As the college student of to-day is the leader of to-morrow we can expect, through the graduates, to spread modern concepts of tuberculosis into the family and community. This fact makes our tuberculosis programs in our colleges and universities a major educational enterprise.

Our attitude in regard to tuberculosis as a contagious disease has changed. Children were known to be susceptible, but for years little or no protection was given to adults. Surveys in medical and nursing schools have shown the danger of spread of the disease to adults, and now steps are being taken—still rather slowly—to correct this.

To summarize briefly the results of statistics we have gathered in the past four years: in general we found each year an average of 6 cases of adult-type tuberculosis per 1,000 college students, and about 30 per cent had positive tuberculin tests. On the basis of one million college students this means 6,000 cases of tuberculosis in serious form, and 300,000 students who have some form of a tuberculous infection as shown by the tuberculin test.

In order to get the true picture of tuberculosis from the age of 15 to 25 years, I like to add to the above figures the results of high-school surveys. These have shown about 1 per cent tuberculosis of the adult type and an average of about 40 per cent tuberculin reactors. There are over 5,000,000 students in our high schools; this means 50,000 cases of adult-type tuberculosis and 2,000,000 students who have a tuberculous infection.

It is difficult to translate these figures into dollars. If we assume that, on the average, one year of sanatorium care at the rate of $1,000 per year will be necessary for each case, then the total cost for high-school

students will be $50,000,000 and for the college group $6,000,000. In addition, it is safe to say that a year out of a high-school student's life will cost at least $1,000 and a year out of a college student's life $2,000. The total cost of tuberculosis in high school would be $100,000,000 and in college $18,000,000 or $118,000,000 for the two groups combined.

This financial side alone is quite enough to make the problem worthy of our serious consideration. If we add to this the human values which are lost through broken lives, blasted hopes, wrecked homes and death, we are justified in laying out a broad program, not only for control, but as we dare say now for the eradication of tuberculosis in these student groups.

As we look backward to 1930 and 1931 we can note the following results which have been achieved:

1: A general recognition of the fact that tuberculosis is a contagious disease, that there is real danger of spread of the infection in adults and that tuberculosis is a serious problem in college students.
2: A widespread and growing interest in the problem by national, state, and local tuberculosis organizations and health units, and various college groups.
3: Sufficient statistical data to show the extent of the problem. This yearly survey should continue.
4: The acceptance of tuberculin testing and X-raying as the best means for the solution of the problem and for evaluating the progress made from year to year.
5: Definite increase in number of institutions where tuberculosis surveys have been made and active programs put in operation.
6: The sectional groups of the American Student Health Association offer a means for stimulating local interest in college health problems and in tuberculosis.

Looking ahead, let me list some of the things still to be achieved:

1: Recognition by college administrative officers and trustees that health work is an important part of a complete educational program.
2: To develop in each of the 1,200 or more institutions, large and small, an efficient health service with adequate funds, facilities and a well trained personnel. The physician in charge should at least have a working knowledge of tuberculosis, its diagnosis, treatment, and symptomatology; he should understand fully the giving of the tuberculin test and its interpretation; as well as the interpretation of chest X-ray films. Only on this basis can a satisfactory program for tuberculosis be built. From the 1936–37 survey by the

American Youth Commission, Doctor C. E. Shepard reports that of the 1,200 institutions only 500 have Health Services. This shows the large amount of pioneer work still to be done in student health.

3: A reduction in the cost of standardized tuberculin (P.P.D.) and X-rays so as to extend their use in developing adequate tuberculosis programs.

4: A more direct linking of the tuberculosis work in colleges with the community by making the college health record available to family physicians and to the appropriate health officers.

5: More extensive use of local and state health units and sanatorium personnel for tuberculosis work in colleges where adequate health services have not been developed. This has been done in many places.

6: More active coördination of tuberculosis work in college with that in high schools. The record of examination of students in high school should be available to college health officers when students enter college and be an integral part of credentials for admission.

7: An accurate follow-up for 5 or 10 years of college students after graduation. Statistics on morbidity and mortality during this period would be helpful in planning suitable health programs in college. A survey at the University of Illinois of 841 deaths from 1916 to 1935 showed that 114 (13 per cent) were due to tuberculosis, 80 men and 34 women. The average time out of college at time of death was 3 years. In one class at an eastern school I have been advised that 7 per cent died of tuberculosis.

8: Lastly, I should like to point out the need for training Health Service physicians in tuberculosis. We ought to have centres at various places where four to six week courses could be given. The requirements for such centres should be:

(*1*) A well organized health service

(*2*) A medical unit, containing a tuberculosis sanatorium or service for instruction in diagnosis, treatment, and X-ray technique and interpretation

(*3*) A large enough student body to give a definite idea of the methods and problems involved in dealing with tuberculosis in students

(*4*) A personnel trained in teaching tuberculosis and also in direct charge of the tuberculosis program at the institution

Such centres probably could very easily be set up at Stanford, Wisconsin, Minnesota, Pennsylvania and Yale.

PHRENICECTOMY REINFORCED BY PNEUMOPERITONEUM[1]

FRANK FREMMEL

Pneumoperitoneum to induce a better pulmonary relaxation following phrenic paralysis was studied in some patients at the Municipal Tuberculosis Sanitarium of Chicago largely as the result of experiences that arose from accidental inflations into the abdominal cavity as well as from knowledge derived from the use of this procedure for other purposes.

When X-ray plates were reviewed it would at times be discovered, particularly when a phrenicectomy had preceded pneumothorax, that a pneumoperitoneum was present. As a result of the earlier years of work with pneumothorax, it can now be readily understood why, when an operator carried a large pneumothorax service without the facilities of fluoroscopy, the peritoneal cavity was inadvertently insufflated instead of the pleural cavity. These accidental inflations were observed at irregular intervals over a period of several years without having produced any particularly adverse symptoms or complications.

In similar inadvertency, one patient had been repeatedly refilled with air into the abdomen. This patient was a female, 21 years old on admission, August 30, 1927, who had a fibrocaseous involvement of the right upper lobe. The course of her illness was stationary until January 8, 1930 when a bronchopneumonic spread started in the right lower lobe. A phrenicectomy was performed April 5, 1930, but the patient's toxicity continued unabated. Pneumothorax was then attempted, beginning August 25, 1930, and given at the usual regular intervals. With this there occurred a progressive improvement in the general condition of the patient. The sputum quantity, which had increased to a cupful, progressively decreased and has been persistently negative since March 10, 1932. Her weight record showed a steady loss from 118 lbs. on admission to 99 lbs. shortly after onset of the acute pneumonic process. With the induction of the pneumothorax treatment, there occurred a general improvement in her symptoms and a steady increase in weight up to 131 lbs. at the time of her discharge.

The patient was given 24 refills. Nothing unusual about the initial manom-

[1] From the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

eter readings was noted; they were −2, −1 after 350 cc. of air had been introduced at the first treatment. The eleventh treatment then showed a paradoxical reading of +2, −1. Again on the twentieth reading there was a +2, 0. The irregularity and undependability of the manometric readings in pneumoperitoneum will again be referred to in a later section of this article.

A review of the X-ray plates showed a large amount of air in the right subphrenic region with clear demarcation of the liver, a condition that could be traced back to the first induction of air, given in the sixth intercostal space. A small amount of air could also be seen below the left diaphragm, in which region the outer border of the splenic curvature was clearly visible. Loops of bowel were likewise in evidence in other plates below the left diaphragm. With the recognition that a pneumoperitoneum had been induced instead of a pneumothorax, it was decided to discontinue the procedure.

During the course of these treatments resorption of the pneumonic process at the base of the right lower lobe, together with fibrosis of the upper lobe, was interpreted from the X-ray plates. The peritoneal air absorbed in two months, but the diaphragm retained its high position of elevation. During the next three years this patient was under the observation of a city dispensary, which reported that she remained in good health, having married and left the city.

A unique experience occurred in a female patient admitted to the Sanitarium in September, 1928. She was 29 years of age. Her onset occurred after childbirth, 14 months before admission. The usual symptoms of pulmonary tuberculosis were present. The physical examination on entrance revealed impaired resonance in the left upper lobe with medium moist râles extending into the lower lobe. The patient also had a tuberculous laryngitis. She did well on rest treatment until February, 1929, when toxaemia increased, dulness of the entire left lung developed, with coarse moist râles throughout, and evidence of a moderately large cavity in the left axillary region was detected. In March, a left phrenicoexairesis was done. Very little improvement in the condition of the patient resulted. The physical findings in the left lung were approximately the same and a pneumothorax was recommended and started in August, 1929. During the next four months the sputum, which had been persistently positive, became negative and was reduced in quantity from two ounces a day to approximately one-half dram. In November, 1930, the pneumothorax was discontinued. The patient was discharged the following month and has been under observation since that time. Her sputum has been continuously free of tubercle bacilli, she now weighs 176 lbs., and has performed her own general housework unassisted for six years. Physical and X-ray findings corroborate that the tuberculous process is arrested.

The X-ray film on admission showed a caseous pneumonic process in the

left lung with a wedge-like infiltrate in the upper part of the lower lobe. The infiltrate appeared to be one of recent origin. Later films disclosed an extension of the pneumonic infiltration in the lower lobe. Following this, phrenicoexairesis was done, resulting in a moderate rise of the diaphragm. Shortly thereafter, a definite area of excavation could be seen in the area where the pneumonic infiltration of the lower lobe had previously been observed. Still later, the areas of excavation appeared to increase until one attained the size of an orange. Also a coarse mottling of the right pulmonary field was observed which was absent in September, 1930, about a year after pneumoperitoneum had been induced. In this film air can be seen below the diaphragm.

On April 9, 1929, an increased rise of the left diaphragm was apparent. This took place following the effort to induce pneumothorax. The first manometer reading was paradoxical, showing zero on inspiration and −5 on expiration. As the therapeutic procedure was continued, it was found that the pleural cavity had been entered and a pneumothorax induced. Now there was present a combination of three collapse procedures: phrenicoexairesis, pneumoperitoneum, and pneumothorax, with a complete collapse of the cavities. Later observation showed resorption of the pneumothorax, a very high rise of the left diaphragm as a result of the pneumoperitoneum, and also a lifting of the right diaphragm. The treatment with pneumothorax, with evidence of pneumoperitoneum, continued until August, 1930, when a high rise of the left diaphragm was observed. It stood at the level of the third rib anteriorly and the seventh rib posteriorly, while the lung had reëxpanded and the pneumothorax was obliterated. The film of November 5, 1936 showed a continuation of the high rise of the diaphragm, fibrotic areas extending through the left lung, no evidence of cavities, and the right pulmonary field clear throughout. Physical findings showed a few scattered râles in the left chest which cleared after coughing. There was no moisture on the right side and the patient raised no sputum.

It appears that the additional rise of the diaphragm induced by pneumoperitoneum was an important factor in closing, and maintaining closed, the large areas of cavitation that had developed. Also the maintenance of a higher elevation of the paralyzed diaphragm is considered to have been a means by which a greater pulmonary rest was secured so that further spread of the tuberculosis was prevented.

Another factor that favored the induction of pneumoperitoneum in pulmonary tuberculosis was the knowledge of the usual steady improvement that occurs after the third month of pregnancy in phthisical patients, as a result of the pulmonary relaxation due to the higher position of the diaphragm produced by increased intraäbdominal pressure. Following delivery, the period of greatest danger for pulmonary tuber-

culosis, renewed activity is known to occur, and this has been attributed largely to the release of the diaphragm as a result of the lowered intra-abdominal tension.

Furthermore, the review of phrenicectomized patients has shown that, when the diaphragmatic rise is high, a better result is more likely to follow, with better relaxation and more rest secured in the treatment of the diseased lung. It is known that the asthenic type of patient, who is undernourished and has a lax abdominal wall, seldom attains a satisfactory rise of the diaphragm. In contrast, a stout, well nourished patient with a firm abdominal wall, in whom the intraäbdominal pressure is higher, attains a more satisfactory rise of the diaphragm and a better therapeutic result. It was observed that, when the rise of the diaphragm was high, paradoxical movement of the paralyzed diaphragm seldom occurred.

Reasonable safety could be assured the patient because of the already established practice of pneumoperitoneum as a diagnostic agent as well as for therapeutic effect in tuberculous enteritis and peritonitis. The observations on incidental pneumoperitoneum with satisfactory clinical results, and on the course of pulmonary tuberculosis during pregnancy, encouraged the intentional use of this method, particularly since previous experiences had shown that it could be used with a reasonable degree of safety. Pneumoperitoneum seemed particularly promising for the stabilization and further elevation of a paralytic diaphragm that was not attaining the desired effect.

It was expected that, with the increased abdominal pressure following the induction of air into the peritoneum, the least resistant portions of the diaphragm would yield to this pressure and thereby bring about a better rise of the diaphragm with a correspondingly greater degree of pulmonary relaxation. In order to insure that the pressure would be focused principally upon the paralyzed diaphragm, the anterior abdominal wall was fortified by the application of a cardboard brace cushioned with an abdominal dressing. This brace was then bound tightly to the anterior wall with an abdominal binder. By this means the tendency to paradoxical movement of the paralyzed diaphragm could be stopped. Not only was fixation of the paralyzed diaphragm secured, but also limitation of the function of the contralateral diaphragm as well. Thereby, a greater degree of rest can be brought about for both lungs, particularly on the side of the paralyzed diaphragm.

METHODS OF ADMINISTRATION

It was necessary to determine the most favorable site for the induction of pneumoperitoneum and the amounts of air that should be injected. Much of this could be deducted from the practice of pneumoperitoneum for other purposes and from experiences with pneumothorax.

For the initial treatment it was decided to enter the peritoneal cavity in the right lower thoracic region at the level of the ninth intercostal space in the midaxillary line. The accident of perforating a hollow viscus would be avoided, as the liver would be a protection in this area. Naturally, insufflation into the abdomen need not necessarily be applied under the paralytic diaphragm for the reason that there are no barriers to prevent an equal distribution of pressure throughout the peritoneal cavity unless previous disease with adhesion has occurred.

The apparatus used has been the same as that for pneumothorax. Before each treatment the patient was carefully fluoroscoped. The refills were conducted similarly to those for pneumothorax. Generally from 200 to 300 cc. of air were insufflated, repeated with equal amount on the second day, and the intervals were gradually increased. The resorption rate appeared to be about the same as that from the pleural cavity.

The unreliability of the manometric readings has already been referred to and is one of the reasons that precaution must be taken to measure the level of the diaphragm by thorough fluoroscopic examination before and after each treatment. It has been noted by Zink and others, particularly in asthenic patients with a weak abdominal wall, that the manometric reading remains negative almost to the end of inspiration, and only tends to a less negative or positive reading at or near the approach of expiration. Probably for this reason, when pneumothorax was intended, the peritoneal cavity has been entered and the operator has observed what appeared to be normal intrapleural readings.

Again it has occasionally been found that, with the first treatment, no fluctuations of the manometer were visible. However, if a local anaesthetic is used, sufficient suction toward the abdomen will be noted to aspirate the novocaine in the needle cap toward the peritoneal cavity. As the treatment is carried on, positive pressures are produced. When pressures of 6 to 8 cm. were reached, it was seen again that no manometric fluctuations took place.

With pneumoperitoneum, the practice has been to maintain a posi-

tive pressure in the abdomen, sufficient to keep the paralyzed diaphragm at rest, and elevated higher than without this procedure in order that a greater degree of pulmonary relaxation might be attained; it was also attempted to eliminate paradoxical movement of the paralyzed diaphragm. The amount of positive pressure utilized is a variable factor depending upon the individual case. The range of pressure has been between +4 and +8 cm. as shown by the water manometer.

DANGERS OF ADMINISTRATION

The dangers of administering pneumoperitoneum have been for the most part discussed by roentgenologists who have used this procedure for diagnostic purposes. As with pneumothorax, so with pneumoperitoneum, air embolism has been a serious danger. If it occurs more frequently than with pneumothorax, the records are not clear. In the series of cases presented herewith, there have been no deaths and one instance of air embolism took place in 218 refills. This patient made an uneventful recovery.

The cause for the air embolism was definitely determined to have been due to the piercing of pulmonary tissue in the costophrenic angle. An X-ray film taken after the accident revealed a small pneumothorax pocket in this area. It is important for the operators to make certain that the needle is definitely below the area of pulmonary tissue. For this reason the diaphragmatic position should be carefully marked with the aid of the fluoroscope before treatment.

Roentgenologists who have used pneumoperitoneum for diagnostic purposes obviously have employed the procedure when some intraäbdominal complaint was present. Therefore, complications from the employment of pneumoperitoneum would take place under conditions not met with in pulmonary tuberculosis, as, for instance, the piercing of an abdominal aneurysm, rupture of a carcinomatous viscus, puncture of a distended kidney pelvis, etc.

The discomforts following the administration have been trivial in character. The patient, with the first treatment, has a feeling of tenseness in the upper part of the abdomen. As the procedure is continued with increased pressures, pain in the upper abdomen is another complaint. When this takes place, the treatment is stopped until the next refill is due. This has not taken place unless the manometer readings were over +4 cm. of water pressure.

Substernal soreness, pain in the shoulder of the nonparalyzed side, and also hiccoughing have been observed. No peritoneal effusions have taken place and no intraäbdominal spread of tuberculosis. Subcutaneous emphysema has been a minor accident similar to the experience with pneumothorax. Dyspnoea, cyanosis, nausea and emesis are symptoms that were present when high intraäbdominal pressures had been employed to the extent that diaphragmatic actions were suspended on both sides.

REVIEW OF CASES TREATED BY PNEUMOPERITONEUM

A small group of cases presenting variable problems that might be assisted by pneumoperitoneum and phrenic paralysis was selected in order to determine whether this method could be beneficially employed for a larger range of conditions than that indicated from the accidental instances of definite improvement in acute basal pneumonic tuberculosis as cited above.

It has been interesting to see the report by L. M. Kugelmeier in *Beiträge zur Klinik der Tuberkulose*, December, 1935, in which he reviewed a case of acute basal pneumonic tuberculosis in a man 30 years of age who had repeated haemorrhages from the lungs and also a moderately severe diabetes mellitus, for which he was given diabetic management. It was first decided to do a phrenic paralysis rather than a pneumothorax because of the acuteness of the tuberculous process. Following the phrenic paralysis, the haemorrhages continued and no improvement occurred. Therefore, an effort was made to induce pneumothorax. After a few treatments, it was found that a pneumoperitoneum had been induced, the paradoxical movement of the paralyzed diaphragm was stopped, and there followed a resorption of the tuberculous exudate, closure of the cavity, negative sputum, and arrest of the disease.

Kugelmeier reviewed other instances of accidental pneumoperitoneum and finally concluded that pneumoperitoneum should be given a trial as a method of treatment for pulmonary tuberculosis in association with phrenic paralysis.

At the Chicago Municipal Tuberculosis Sanitarium, there have been eight cases observed for a period of 6 to 18 months.

The first case selected for treatment was a patient, age 34 years, whose onset was catarrhal in June, 1929. On admission there was a right upper lobe

tuberculosis with cavitation, complicated by a questionable tuberculous laryngitis. Right pneumothorax was tried, failed, and was followed by phrenicoexairesis and an upper stage thorocoplasty. The sputum remained positive. Six months later, in April, 1935, pneumoperitoneum was induced and continued for two months. Physical findings prior to the pneumoperitoneum elicited moist râles in the lower right lobe near the hilum which disappeared shortly after the pneumoperitoneum was instituted. The patient's sputum became negative, following which she was discharged from the hospital. She continues under observation, her sputum remains negative, and the symptoms and physical findings indicate an arrested lesion.

A second patient entered the Sanitarium in September, 1930, at 25 years of age. Clinical diagnosis on admission was minimal B tuberculosis, with moist râles in both apices. However, on X-ray examination the entire upper right field was found mottled and the extent of the disease was moderately advanced. In September, 1932, a right pneumothorax was attempted and proved unsatisfactory. In October, 1932, a right phrenicoexairesis was performed. There had developed by that time a cavity in the right upper lobe which was uninfluenced by the phrenicoexairesis. In February, 1934, an upper stage thorocoplasty was done. The patient continued to have a positive sputum and evidence of moisture in the right hilum region. A left pneumothorax was started which produced a lower selective collapse. Nevertheless, the sputum remained positive. Therefore, it was decided to try a pneumoperitoneum, especially since moisture could be heard on the right side near the hilum. Pneumoperitoneum was started October 29, 1935, and is still maintained. The patient's condition is unchanged and there is no permanent suppression of the positive sputum.

The third patient was 18 years of age on admission in May, 1935. Before her admission to the Sanitarium, pneumothorax had been tried in March, 1935 and was followed by a phrenicoexairesis in April, 1935. The onset had been catarrhal the previous October. Physical findings were posttussive râles and increased whispered voice with consonating râles posteriorly in the lower lobe region close to the spine. An X-ray film showed infiltration of comparatively recent origin without cavitation. The question of a thorocoplasty arose after several months of observation because her sputum remained positive. In order to be successful, a complete thoracoplasty was deemed necessary because of the location of the process. It was considered to be a radical procedure in view of the limited involvement. Pneumoperitoneum was decided upon, instituted in October, 1935, and continued until April, 1936. After the seventh treatment, the patient's sputum became negative and has remained so. It was in this patient that the costophrenic angle was penetrated which resulted in an air embolism.

A colored patient, age 31 years, was the fourth case in this series. She gave a history of onset of tuberculosis in October, 1929. In March, 1930, pneumothorax was started and continued on the right side until June, 1933. Then, as the result of an obliterative pleuritis which followed fluid formation, the lung reëxpanded and in November, 1935, a right phrenic paralysis was performed. Physical findings were those of an extensive involvement with cavitation throughout the right lung, corroborated by X-ray plates and fluoroscopy, showing little rise of the right diaphragm. The 24-hour sputum quantity averaged 140 grams. Pneumoperitoneum was tried rather than thoracoplasty because the patient was decidedly overweight (182 lbs.) and was not considered a good operative risk. Pneumoperitoneum was continued for three months. There was a moderately increased rise of the diaphragm, a reduction of the sputum quantity to 65 grams, without any other evidence of improvement. It was obvious that the procedure would not control the extensive amount of involvement, so it was discontinued and the patient was recorded as unimproved.

In the next patient with a bilateral pulmonary involvement, pneumothorax was attempted on both sides and failed, after which a phrenic paralysis was performed on the left side where an apical cavity was present. This patient entered the Sanitarium in May, 1935 with a history of a catarrhal onset in October, 1932. The patient also had an early tuberculous enteritis. Fluoroscopy showed paradoxical movement of the left diaphragm with practically no elevation. In February, 1936, pneumoperitoneum was started and has been continued with improvement, such as reduction in the size of the cavity on the left side and resorption and increased fibrosis in the right pulmonary field. The enteritis improved. The sputum remained usually positive on concentration tests.

In May 1931, a 15 year old girl entered the Sanitarium with an extensive bilateral caseous cavernous tuberculosis. On rest treatment there was a progressive improvement in the symptoms as well as physical findings. A left pneumothorax was started in March, 1934. A right pneumothorax was begun in July, 1934. Bilateral pneumothorax was carried on with satisfactory selective collapse on the right side, but an imperfect one, because of adhesions, on the left side. The left pneumothorax was therefore discontinued and a left phrenic paralysis was performed. Very little rise of the diaphragm resulted, with paradoxical movement. Pneumoperionteum to reinforce the phrenic paralysis was instituted in March, 1936. At this time considerable fibrosis was present in both lungs. In the left upper lobe there was a medium-sized cavity with a thick wall. An obliterative pleuritis caused reëxpansion of the right lung, and pneumothorax was discontinued in March, 1936. The pneumo-

peritoneum has succeeded in producing a higher rise of the left diaphragm, but has not had any influence in closing the cavity. Because of an extensive bilateral fibrosis, the cardiorespiratory reserve of the patient was in a state of delicate balance, readily disturbed, with fixation of both diaphragms caused by a positive pressure in the pneumoperitoneum. This resulted in cyanosis, nausea and emesis. The patient has stated that the pneumoperitoneum decreases her cough and helps her to bring up sputum with less effort. This patient is classified as unimproved.

The seventh patient was admitted to the Sanitarium in September, 1929. The physical findings were those of a bilateral, moderately advanced tuberculosis without complications. The X-ray film showed a questionable cavity in the right upper lung region. In October, 1933, right pneumothorax was started, at which time a definite cavity presented itself in the right hilum region. Pneumothorax was continued until October 20, 1934, without successfully closing the cavity. Lung reëxpansion occurred as the result of adhesions and obliterative pleuritis. In August, 1935, a right phrenicoexairesis was done to assist in the closure of the cavity. There followed a progressive distention of the cavity to the size of three and a half inches in length by two inches in breadth as measured on the X-ray films. On May 12, 1936, pneumoperitoneum was started. At this time, the cavity wall was heavily fibrosed. A high rise of the diaphragm was secured with relaxation of the pulmonary tissue around the cavity, and a slow but progressive decrease in the size of the cavity was observed. The quantity of sputum was reduced from 86 grams daily to 32 grams. A thoracoplasty was not resorted to because of the amount of fibrosis and tuberculous involvement of the better lung. This patient can be considered as improved by the treatment.

The last patient, 36 years of age, entered the Sanitarium in May, 1935, with a far advanced bilateral tuberculosis. The onset was with pleuritis in October, 1930, with an effusion on the right side. Because the X-ray film showed more involvement on the right side than on the left, pneumothorax was attempted on this side, but failed because there was no free pleural space. A phrenic paralysis was performed in July, 1936. There was a paradoxical movement of the diaphragm with very little rise. In January, 1936, a pneumoperitoneum was begun and continued until July, 1936. The sputum became negative following this treatment, and resorption of the exudative tuberculous process in the right upper lobe was noted both by physical findings through disappearance of moist râles, and by X-ray studies that showed a reduction of the infiltrative lesions on both sides, particularly the right. This patient was discharged in July, 1936 and continues in good health.

INDICATIONS FOR REINFORCEMENT OF PHRENIC PARALYSIS BY PNEUMOPERITONEUM

With the limited experience on only a few patients, it seems impossible to establish, as yet, definite indications for this treatment. Of the eight patients treated, three are apparently arrested, two can be considered as improved and the remaining three as stationary. Four of them still continue treatment. There have been no tuberculous complications or acute extensions of the pulmonary involvement during the course of treatment.

One opinion reached has been that pneumoperitoneum has a definite retarding influence on the pulmonary spread of the disease. If this conclusion be sound, then the procedure may be of value to inhibit an acutely extending tuberculous disease, especially in patients who may have a pneumonic involvement on one side with an associated new extension on the other. Under such conditions, it is frequently inadvisable to induce pneumothorax, particularly when bilateral treatment is required.

Phrenic paralysis with pneumoperitoneum would assist to rest both lungs, more on the side of greater involvement. This conclusion is supported by several accidental experiences cited above, in which remarkably prompt arrest of tuberculous pneumonia was seen after pneumoperitoneum.

It may also be suggested that in indurated chronic tuberculosis of several years' standing, the influence of pneumoperitoneum would probably be negligible. Also, if the diaphragm has been definitely and strongly fixed by pleuritic involvement, no result from this procedure could be expected. The more extensive the adhesions between the parietal and the visceral pleurae, the lower the level, and the greater the circumference of the pleuritic adhesions, the greater would be the interference to diaphragmatic rise and pulmonary relaxation.

The third case of the series affords an example of pneumoperitoneum fitting the occasion for this particular collapse method. It illustrates an early basal infiltrate that could not be controlled by pneumothorax because of pleural obliteration, and which was not sufficiently relaxed by phrenicoexairesis.

It may be questioned whether an abdominal binder alone, without the assistance of pneumoperitoneum, might not give similar results. This seems to be sound logic and is an application to support phrenic

paralysis which is not sufficiently utilized. Nevertheless, observation demonstrated that, with pneumoperitoneum and abdominal binder, the position of the diaphragm was kept at a higher level. During the interval between treatments, as the air was resorbed, it was seen that diaphragmatic lowering resulted.

An observation of revealing significance was that after a period of treatment with pneumoperitoneum the diaphragm continued to stay at a higher level than was produced by phrenic paralysis alone. Particularly was this shown by the two cases of accidental inflation where, in one instance, after 6 years, the diaphragm remained at rest in a position of high elevation. In the first patient only 13 refills were given. Nevertheless, the diaphragm was noted recently, about 18 months after discontinuance of the procedure, to be fixed in a position approximately two inches higher than before pneumoperitoneum was instituted. In the case reported by Kugelmeier, only three refills were necessary to fix the diaphragm sufficiently and bring about resorption of a caseous pneumonic basal tuberculosis and an apparently permanent arrest of the disease.

How long should pneumoperitoneum be administered? The answer to this question can be reached only by further experience. Naturally, if results can be secured in a few administrations, the danger from accidental complications is largely diminished. It may be suggested that after the operator has attained the greatest rise consistent with the condition of the patient, the intervals between treatments be extended and, providing the diaphragm remains secured at the higher level, pneumoperitoneum be discontinued.

In several of the patients in this series, the procedure has been carried on for over six months. This was done to find whether prolongation of the treatment would bring about a progressive improvement. In the seventh case, there was a large centrally located cavity off the hilum that has been gradually closing after 7 months of treatment. Pneumoperitoneum will be continued for further observation.

It may be stated with firm belief that in acute lesions of short duration, if the lung can be kept in relaxation and at rest, healing will take place more promptly and with better end-results. This is knowledge acquired from the application of the various collapse measures in pulmonary tuberculosis. The older the lesion, the greater the possibility for complications preventing a good collapse, and therefore the less prompt and certain the results. The third case, with an early basal

infiltrate that responded quickly to pneumoperitoneum, in contrast to the sixth case where the duration of the process covered a period of several years, bears out the above statement. Basal lesions of recent origin apparently can be most favorably influenced by this treatment.

As previously indicated, in more apically situated lesions, success depends upon the degree and position of any existing pleural adhesions. Extensive, firm, low-placed adhesions would prevent useful application of this procedure.

In regard to the closure of cavities, pneumoperitoneum to reinforce phrenic paralysis should be more useful in cases of small, recent, thin-walled excavations, not firmly fixed by pleural adhesions, than in instances of old, large, indurated cavities, fixed by adhesions.

Pneumoperitoneum may be indicated as an emergency measure in haemoptysis when phrenicoexairesis has been performed and pneumothorax has been tried and failed. Thoracoplasty does not lend itself readily to this type of an emergency.

If enteritis complicates pulmonary disease associated with an unsatisfactory phrenic paralysis, reinforcement of the diaphragm by pneumoperitoneum may benefit both conditions.

SUMMARY

This preliminary investigation of the value of phrenic reinforcement by pneumoperitoneum, as another aid in the collapse therapy program for pulmonary tuberculosis, led to the following observations and conclusions.

The inadvertent administration of pneumoperitoneum where pneumothorax was intended has been harmless, and, on several occasions in pneumonic lower lobe tuberculosis associated with phrenic paralysis, has led to an early arrest of the disease.

The use of pneumoperitoneum for other purposes has been a relatively safe procedure.

Certain suggestions from the above reported eight cases are made for the method of treatment and the selection of patients for this therapy.

Finally, it can only be stated with reservation pending further experience that pneumoperitoneum to reinforce phrenic paralysis is based upon a logic worthy of continued investigation.

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PLATE 1

FIGURES 1A, B, C and D are of the same case.

FIG. 1A. September 21, 1928. A phrenicectomy has been done for an extensive involvement.

FIG. 1B. August 21, 1929. Pneumothorax induced. There is a large excavation present.

FIG. 1C. October 15, 1930. Accidental pneumoperitoneum not recognized following several refills, though pneumothorax was intended.

FIG. 1D. November 5, 1936. Six years later. Sputum continuously negative. Diaphragm highly elevated. No activity.

FIGURES 2A, B and C are of the same case.

FIG. 2A. January 9, 1930. A caseous pneumonic right lower lobe involvement with excavation after phrenicectomy.

FIG. 2B. September 3, 1930. Two months later. An accidental pneumoperitoneum induced instead of pneumothorax.

FIG. 2C. February 2, 1933. Three years later. Diaphragm remains high. Sputum is negative. No evidence of clinical activity.

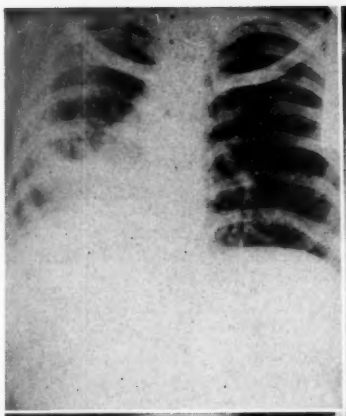

FIG. 1A

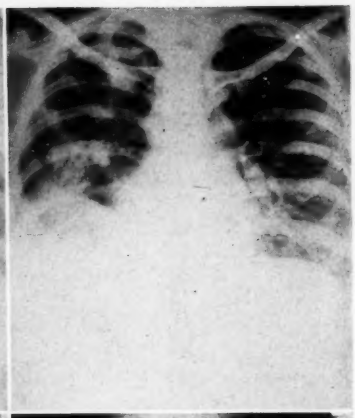

FIG. 1B

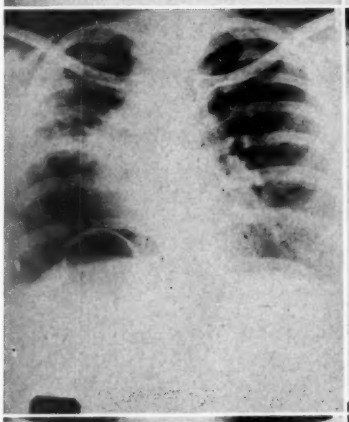

FIG. 1C

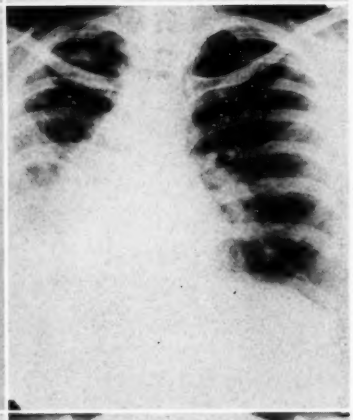

FIG. 1D

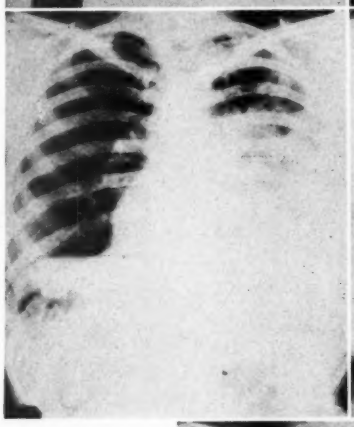

FIG. 2A

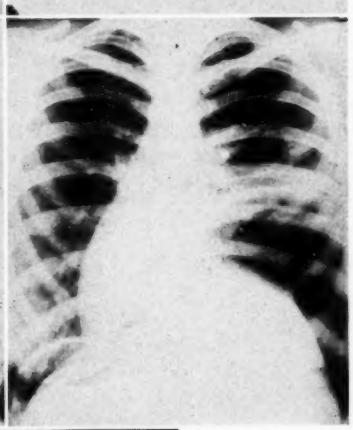

FIG. 2B

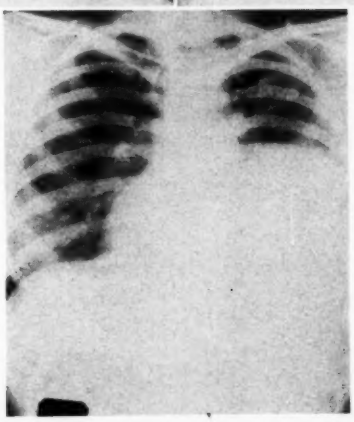

FIG. 2C

PLATE 1

PLATE 2

FIGURES 3A, B, C and D are of the same case.

FIG. 3A. May 13, 1935. Phrenicectomy for right lower lobe lesion with excavation. Pneumothorax tried and failed.

FIG. 3B. November 26, 1935. Intentional induction of pneumoperitoneum with resorption of basal exudate.

FIG. 3C. February 25, 1936. Three months after pneumoperitoneum induction. Patient has negative sputum and no clinical activity.

FIG. 3D. December 4, 1936. Six months after discontinuance of pneumoperitoneum. Sputum still negative and there is no evidence of clinical activity.

FIGURES 4A and 4B are of the same case.

FIG. 4A. April 5, 1935. Two and one-half years after a right phrenicectomy.

FIG. 4B. December 15, 1936. Six months after intentional pneumoperitoneum. Cavity one-third original dimension. Clinical improvement.

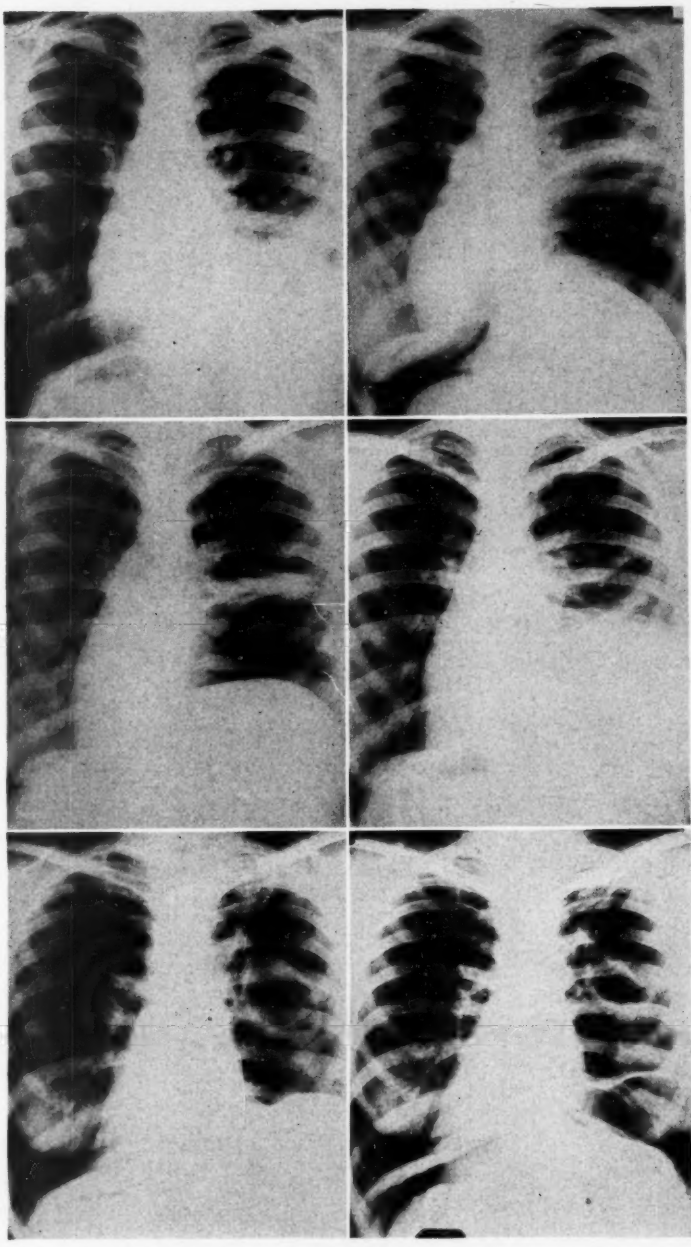

FIG. 3A FIG. 3B

FIG. 3C FIG. 3D

FIG. 4A FIG. 4B

PLATE 2

PULMONARY REST BY LIMITATION OF COSTAL AND DIAPHRAGMATIC EXCURSION[1]

ARTHUR BRUCE STEELE

The importance of pulmonary rest in the healing of a tuberculous lesion has been constantly emphasized by phthisiologists. The traumatizing effect of respiratory movements advanced first by Forlanini has stimulated the application of measures to inhibit this wear and tear on the diseased lung. In addition to the limitation of respiratory function by complete bed-rest many adjuncts have been successfully used for immobilization of the lung. Of these, artificial pneumothorax, phrenic nerve interruption and various forms of thoracic surgery have been most universally successful in application of the above enunciated principle of rest. Sir Arthur Keith (1) in 1908 estimated that the lung usually works at 10 per cent of its capacity and in persons of sedentary occupation only at 5 per cent. Pulmonary rest has recently been defined (2) as absence of volumetric change.

It is understood that the mechanics of respiration are composed of costal (horizontal) and diaphragmatic (vertical) respiration. Any limitation of either type must have an effect on some component of the vital capacity. This limitation is compensated for in the homolateral or contralateral lung for all practical purposes until the subtidal component is markedly reduced. Graham (6) quotes a table from Wilson's (4) paper in which independent workers measured the volume of respired air affected by the action of the ribs and diaphragm respectively. These authorities estimate that costal respiration takes care of 53 to 70 per cent of the total vital capacity.

Paralysis of the hemidiaphragm first reported by Stuertz (3) of Cologne in 1911 initiated a means of limiting vertical respiration. The monograph by Wilson (4) gives a most comprehensive study of the efficiency of this surgical procedure in its effect on respiratory function. The reduction of negative intrapleural pressure by this procedure indicates the direct relaxation of elastic tension in the lung. Volumetric

[1] From the Tuberculosis Division, Santa Barbara General Hospital, Santa Barbara, California.

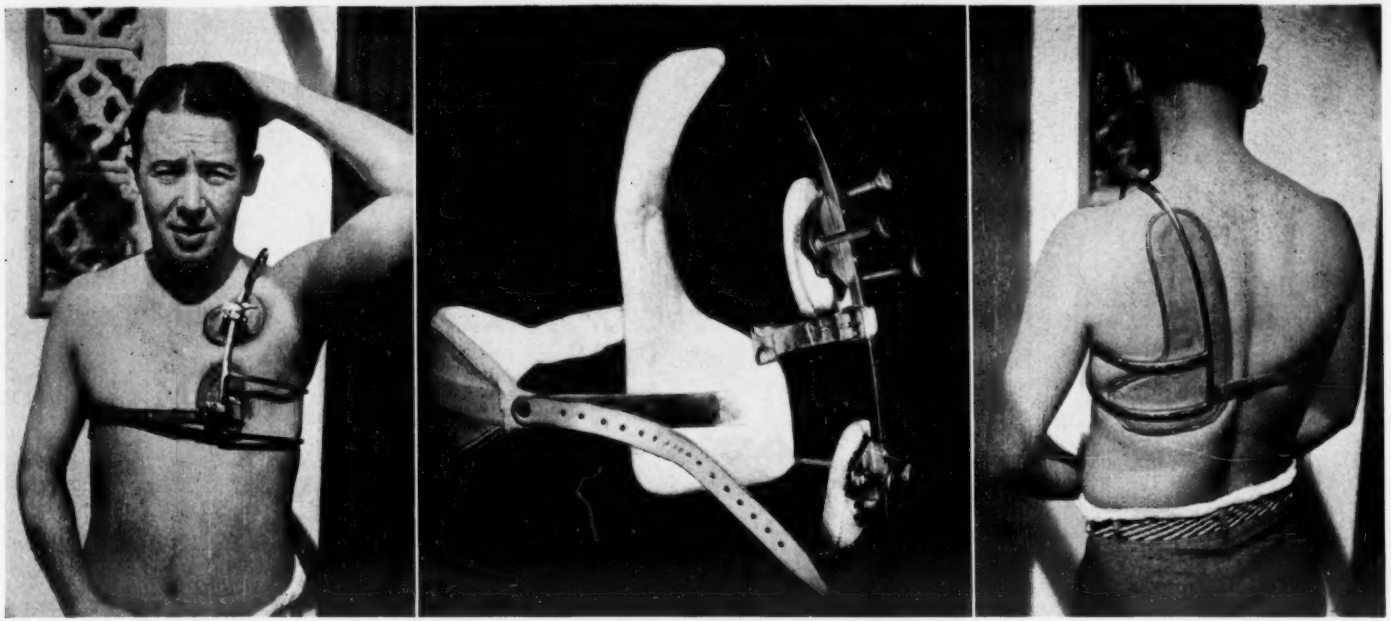

FIG. 1A FIG. 1B FIG. 1C

FIG. 1. Front and back view of the brace in position on the thorax. The rigid hinged band encircling the right chest allows free costal movement on that side.

change is consequently reduced by this means. The lowering of vital capacity by phrenic nerve interruption similarly indicates diminished volumetric change on the homolateral side.

The limitation of the hemithoracic costal respiration has been much more difficult to approach than the diaphragmatic factor. Injections of the intercostal nerves with alcohol, the placing of heavy sand bags on the anterior chest, the effect of posture as advocated by Webb, Forster, and Houck (5) and more recently by Pierson and Newell (2), have been used for this purpose with various degrees of success.

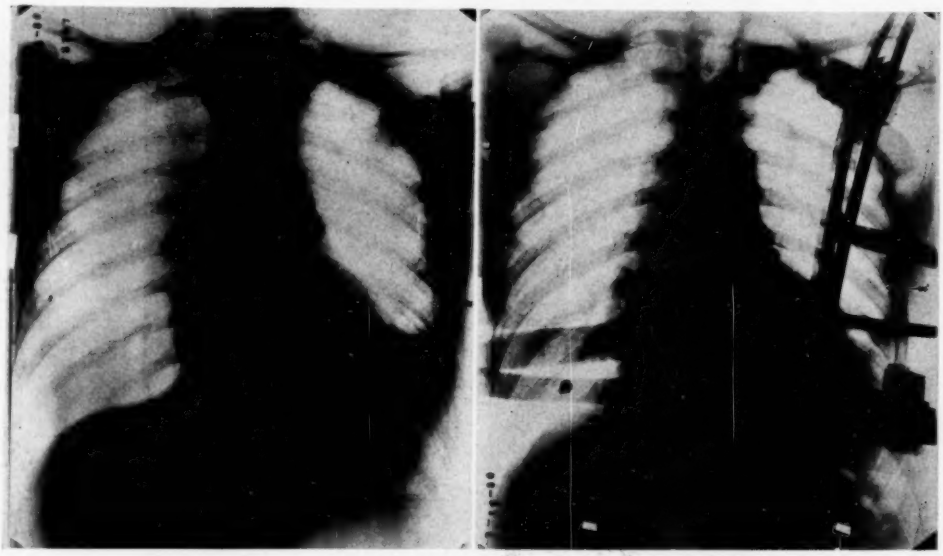

FIG. 2A FIG. 2B

FIG. 2. Double exposure roentgenograms taken in inspiration and in expiration with the brace off and on. Please note the marked costal movement with brace off as compared to that with the brace on as indicated by the arrow.

A practical brace for limitation of costal respiration is here presented (figure 1), the efficiency of which has been measured by two criteria, namely, vital capacity readings and roentgenographic studies with two exposures, one in inspiration and one in expiration, showing the limitation of costal movement with the brace on as distinct from those with the brace off (figure 2).

Table 1 shows in readings of vital capacity the effect of phrenic nerve evulsion limiting thereby vertical respiration, and the effect of the im-

mobilization of costal respiration (horizontal respiration) by pressure from a practical efficient brace. As will be noted, the limitation of costal respiration reduced the vital capacity one-third, about 1,000 cc., before phrenic nerve interruption. Phrenic nerve interruption alone reduced it about 500 cc. Both therapeutic measures applied together reduced the vital capacity about 1,200 cc. All readings are compared in five postures in table 1.

It is appreciated that the pulmonary reserve and compensatory mechanisms which allow for such unilateral immobilization enable adequate respiratory function in this as in other methods instituted to limit pulmonary movement. If rest may be defined as absence of volumetric change this combination offers an adequate manner of procuring maximum rest. The contralateral thoracic movement is in no way inter-

TABLE 1

Vital capacity readings taken in five different positions

	BEFORE PHRENICOTOMY		AFTER PHRENICOTOMY	
	Without brace	With brace	Without brace	With brace
Standing	3,100	2,100	2,575	1,960
Sitting	3,075	2,175	2,485	1,900
On back	2,950	2,000	2,275	1,585
On right side	2,875	1,950	2,575	1,575
On left side	3,000	2,175	2,400	1,765

B.M.—Ht. 5'11"—Wt. 168 lbs.—Normal V.C. 4,800 cc.

Note the effect of the brace and phrenic nerve interruption singly and together on the original vital capacity.

fered with, the rigid hinged band encircling this side of the thorax riding free from the anterior chest wall. If properly fitted and adjusted to the individual thorax there is no discomfort and within a short space of time those subjective sensations of distress known only to the tuberculous patient ("hollow feeling" as expressed by many patients) are eliminated when firm uniform pressure is applied to the ribs on the affected side. Especially is this true if a cavity of moderate dimensions is present. Moreover, this means has the advantage of allowing the patient to recline in any position, permitting free movement of the arms. Tidal exchange is not affected by full application of the brace. Careful graphic estimations were made on patients while recording the respiratory excursions on a revolving drum. But the complementary or subtidal division of the vital capacity is markedly reduced.

The indications for adaptation of this combination singly or together are obvious: wherever and whenever more complete limitation of pulmonary movement is desired.

CONCLUSIONS

1. A means of limiting costal respiration is presented, which, in conjunction with phrenic nerve interruption, offers a most efficient means of immobilization of one lung.

2. Vital capacity readings before application of these measures, singly and together, were made, showing reduction with each and a more complete reduction, over one-third of the original vital capacity, by application of both.

3. Double exposure roentgenograms were made showing uniformly marked costal excursions bilaterally followed by similar exposures showing very negligible costal excursion on the side on which the brace is applied.

4. The means of immobilization here suggested, that is, temporary phrenic nerve interruption with application of the brace, has the distinct advantage that both measures are revocable.

I am indebted to Dr. Philip King Brown, San Francisco, for his helpful suggestions in preparing this paper.

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THE VARYING DURATION OF THE ARRESTED STAGE[1, 2]

A Plea for the Revision of the Present Classification Standards

LOUIS H. FALES AND E. A. BEAUDET

One of the problems that still confronts the phthisiologist is the high mortality rate and the large percentage of reactivation of patients discharged from our tuberculosis sanatoria.

In order to learn more as to the gravity of the situation and to get a line on certain phases of the situation, the following questionnaire was sent to about sixty of the representative sanatoria of the country.

1. What criteria do you use to determine the arrestment of your tuberculous cases?
2. What criteria do you use to determine when a tuberculous patient is ready for discharge from the sanatorium?
3. Have you any data available as to what percentage of your patients discharged as arrested have again become activated?

Replies were received from 58 per cent of those to whom we sent the questionnaire. A summary of answers from those who responded, showing what they considered the criteria in order of their importance for determination of arrest, follows:

1:	Radiographs	90 per cent
2:	Constitutional symptoms	78 per cent
3:	Sputum	74 per cent
4:	Graduated exercise	61 per cent
5:	Physical signs	26 per cent
6:	Blood studies	22 per cent
7:	Sedimentation rate	20 per cent
8:	Guinea-pig inoculations	6.4 per cent

It should be noted that the X-ray stands at the head of the list in importance, it having been mentioned by 90 per cent. Constitutional symptoms ranked second, while sputum came third.

[1] Presented before the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Sanatorium Association at Madison, Wisconsin, September 12, 1935.

[2] Published with the permission of the Medical Director of the Veterans' Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

In this paper we will discuss only the radiographic criteria for arrest and discharge, especially the radiographic specifications for arrest as found in the classification of the National Tuberculosis Association. Here are shown what were considered the radiographic criteria for arrest and discharge by those who answered the questionnaire.

1: Radiographic criteria for arrest:
- a. A healed lesion ..... 32 per cent
- b. A retrogressive or improving lesion ..... 44 per cent
- c. X-ray not used or no criteria given ..... 18 per cent
- d. Answers indefinite ..... 6 per cent

2: Radiographic criteria for discharge:
- a. A healed lesion ..... 26 per cent
- b. A retrogressive or improving lesion ..... 50 per cent
- c. X-ray not used or no criteria given ..... 18 per cent
- d. Answers indefinite ..... 6 per cent

In studying the above, it is to be noted that there was a considerable difference in opinion. While 44 per cent believed that the proper radiographic criterion for arrest should be a retrogressive or improving lesion, 32 per cent held that it should be what appeared to be a healed lesion.

In answer to the third question, as to statistics, 63 per cent gave no data, 20 per cent gave some approximate estimates, while from 17 per cent definite data were obtained.

As the statistics were somewhat meagre as to the after-results attained by patients discharged with radiographically healed lesions, a study was made of a hundred cases discharged from the Veterans' Facility, Livermore, California, during the last nine years, with what appeared to be healed lesions. A description of the hundred cases at the beginning of treatment follows:

1: Race—White ..... 96 per cent
Filipino ..... 3 per cent
Colored ..... 1 per cent
2: Sex—Male ..... 100 per cent
3: Average age—36.7 years
4: World War Veterans—100 per cent
5: Surgical compression—None
6: Bilateral involvement—51 per cent
7: Sputum positive—39 per cent
8: With cavitation—31 per cent
9: With extrapulmonary complications—13 per cent
10: With constitutional symptoms—81 per cent

It should be mentioned that of the hundred cases, twenty-eight were minimal, forty-four moderately advanced, and twenty-eight far advanced. The thirty-one cavities ranged in size from 6 to 2 cm. The above hundred cases were selected as they came, except that three things were deemed essential for our purpose: (*1*) That none were selected unless found to be definitely active at the beginning of treatment. (*2*) That in none had chest surgery been resorted to as an aid to treatment. (*3*) That none were discharged at the end of treatment until the patient had what we considered to be a radiographically healed lesion.

A study of the hundred cases discharged with radiographically healed lesions demonstrated the fact that there was great variability in the retrogression and healing of tuberculous lesions.

1: Constitutional symptoms:
- a. Shortest time to disappear—30 days
- b. Longest time to disappear—3 years, 2 months
- c. Average time to disappear—7 months, 18 days

2: A healed lesion (radiographically):
- a. Shortest time to attain—10 months, 11 days
- b. Longest time to attain—5 years, 8 months, 19 days
- c. Average time to attain—1 year, 11 months, 25 days
- d. A minimal case to attain—1 year, 11 months
- e. A far advanced case to attain—2 years, 6 months
- f. Average time for cavity cases to attain—2 years, 6 months, 11 days

We wish here to especially emphasize the fact that while it took on the average of 7 months and 18 days for the constitutional symptoms of our one hundred cases to disappear, it required an average of two years to attain a radiographically healed lesion.

In the following list may be seen the time required to attain a radiographically healed lesion from a different point of view:[3]

In less than one year	9
From 1 to 2 years	47
From 2 to 3 years	33
From 3 to 4 years	6
From 4 to 5 years	3
From 5 to 6 years	2

[3] In this study we considered a lesion to be radiographically healed when serial roentgenograms showed it to be stationary, the lesion having a hard appearance and with clear-cut margins.

It was found that of the hundred cases, 89 per cent showed radiographically healed lesions in less than three years. Of the eleven cases that took longer, most of them had very extensive involvement.

Finally the following questionnaire was sent to each of these hundred cases. The idea was to find out as nearly as possible how many had become reactivated and how many had died.

1. Since discharge from hospital, has any doctor stated that your tuberculosis had again become active?
2. If so, please state name and address of physician.
3. Have you been able to work since leaving this hospital? If so, the kind of work and the number of hours.
4. Is your temperature normal? If not, how long have you had elevation of temperature?
5. How do you feel? Sleep? Appetite?
6. To your knowledge has your sputum been positive for tubercle bacilli since leaving the hospital?

A summary of the answers to the above questionnaire follows:

Answered questionnaire	81
Reactivated	8—9.9 per cent
Number working	59
Number not working but apparently able to work	12
Working or able to work	73—90 per cent
Reported having positive sputum	5
Occasional elevation of temperature	6
Dead, suicide	1
Dead, due to tuberculosis	1—1.3 per cent

When the first returns came in, fourteen patients reported as having become reactivated. After considerable correspondence with their physicians and the Regional Offices which had their case files, no evidence of reactivation could be demonstrated in six, leaving eight with indications of an active lesion. Of these eight, only one had definite constitutional symptoms. One had suffered a pulmonary haemorrhage with the appearance of a new area of infiltration. In the remaining six, activity was demonstrated mainly radiographically by the appearance of new areas of infiltration, the constitutional symptoms being absent or very slight.

The statistics obtained from those who answered the questionnaire as to the after-results attained at the various sanatoria may be seen in

table 1. They are based on nineteen hundred cases and should merit some attention.

Table 2 shows in more concise form the essential points brought out in table 1.

Tables 1 and 2 seem to show that when a radiographically healed lesion is taken as the criterion of arrest and discharge, fewer reactivations and deaths occur. The fact that 44 per cent of those who answered the questionnaire believed that the proper criterion for arrest is a retrogressive lesion, and 50 per cent believed that a retrogressive lesion is the proper criterion for discharge, it would seem that we have the main answer as to why so many reactivations and deaths occur after discharge.

A retrogressive lesion gives little assurance that a patient is prepared for the resumption of the strain of active life.

The criteria for quiescence and arrest as outlined by the classification of the National Tuberculosis Association Diagnostic Standards, 1936, are:

Quiescent:

1: All constitutional symptoms absent
2: Sputum, if present, negative or positive for tubercle bacilli
3: X-ray findings compatible with a *stationary or retrogressive lesion*
4: The above to have existed *two months*, during the *last month* of which the patient has been taking *one-half hour* walking exercise twice daily, or its equivalent

Arrested:

1: All constitutional symptoms absent
2: Sputum, if present, negative for tubercle bacilli
3: X-ray findings compatible with a *stationary or retrogressive lesion*
4: The above to have existed for *six months*, during the *last two* of which the patient has been taking *one hour's* walking exercise twice daily, or its equivalent

In the above classification, quiescence and arrest are specified as important landmarks on the road to recovery. The only difference between the criteria of these two conditions is that to qualify for the latter status, a negative sputum and more exercise are required. The radiographic criteria are the same. Considering the dependence that physicians are placing on the X-ray in diagnosis and treatment of tuberculosis during the last ten years or more, it is hard for us to understand why it is not given a place of importance in the National Classification.

TABLE 1

A summary of results attained at various sanatoria

NAME OF SANATORIUM	X-RAY CRITERIA FOR		CLASSIFICATION OR STAGE ON DISCHARGE	NUMBER OF CASES	LATER RESULTS	PERIOD OF OBSERVATION
	Arrest	Discharge				
North Carolina Sanatorium	A healed lesion	Variable	Minimal arrested	60	Living and working, 54, or 90 per cent Dead, none	Over a period of 12 years
			Minimal apparently arrested	418	Living and working, 373, or 89 per cent Dead, 21, or 5.5 per cent	
			Minimal quiescent	238	Living and working, 200, or 84 per cent Dead, 18, or 8 per cent	
			Moderately advanced, arrested	15	Living and working, 13, or 87 per cent Dead, none	
			Moderately advanced, apparently arrested	69	Living and working, 58, or 84 per cent Dead, 9, or 13 per cent	
			Moderately advanced, quiescent	659	Living and working, 357, or 54 per cent Dead, 211, or 32 per cent	
Gaylord Farm Sanatorium	A healing lesion	A healing lesion	Minimal, apparently arrested	387	Dead, 10 per cent	Over a period of 20 years
			Moderately advanced, apparently arrested		Dead, 15 per cent	
			Far advanced, apparently arrested		Dead or lost, 50 per cent	

River Pines Sanatorium	A healed lesion	A healed lesion	Arrested, all types	Not stated	Reactivation approximately 10 per cent	Not stated
Barfield Sanatorium	An improving lesion	A healed lesion	Arrested, all types	Not stated	Reactivation less than 5 per cent	Not stated
Metropolitan Life Insurance Co. Sanatorium	Improving lesion	Improving lesion	Arrested, early types	Not stated	Dead, not stated Reactivation, 16 per cent	Not stated
Veterans' Administration Facility, Livermore, California	A healed lesion	A healed lesion	Minimal arrested	81	Reactivation 5 per cent	Last 9 years
			Moderately advanced, arrested		Reactivation 10.8 per cent	
			Far advanced, arrested		Reactivation 14.3 per cent	
					Total number reactivated, 8, or 9.9 per cent Working or able to work, 73, or 90 per cent Dead, 1	

The X-ray specification (no. 3) under both Quiescent and Arrested is, "X-ray findings compatible with a stationary or retrogressive lesion." This of course tells us next to nothing as to the condition present or the progress made between the two stages. What is meant by a stationary lesion is not clear. It can hardly mean a healed lesion as a healed lesion is usually considered not only a stationary lesion as determined by serial roentgenograms, but one that appears radiographically hard and with densities having clear-cut margins. A retrogressive lesion means of course an improving lesion and is a pathologically active lesion.

Under specification no. 4, Arrested, we find, "The above (meaning nos. 1, 2 and 3) to have existed for a period of six months." That is, a patient with a retrogressive lesion on entering the quiescent stage will in six months qualify as an arrested case, provided specifications no. 1 and 2 still hold true.

TABLE 2

Comparison of results of treatment of patients discharged with healed lesions and retrogressive lesions

CONDITION ON DISCHARGE	NUMBER OF CASES	DEAD	PER CENT
Quiescent and apparently arrested	1,771	359	20
Apparently arrested	874	121	13.8
Radiographically healed lesion	156	1	0.6

It was shown earlier in the discussion that the constitutional symptoms of our hundred cases disappeared on the average in seven and a half months, while it required a total of twenty-four months, or sixteen and a half months more, to attain what appeared to us to be a radiographically healed lesion. As just stated, the National Classification provides that a quiescent case may qualify for arrest after a six months' period. The difference between sixteen and a half months and six months explains why so many of the cases coming to the arrested stage according to the National Classification are prone to reactivation; they have been under treatment for too short a time for sufficient resolution and fibrosis to take place.

In other words, a six months' period of treatment after the quiescent stage is reached guarantees little, only an improved lesion. A radiographically healed lesion, on the other hand, which may be attained on the average in ten or twelve months more of treatment, guarantees a

minimum amount of reactivation and a posthospitalization mortality of almost zero.

Why, may we ask, should a six months' period of time or any period of time be one of the criteria to qualify for the arrested stage? Such practice might have been justified thirty years ago when there was little to determine the progress of tuberculous cases. To-day, however, with serial stereoroentgenograms at our disposal, it would seem that the need of a specified period of time to qualify for arrest should be discarded as one of the relics of the past.

In regard to specification no. 4 under both Quiescent and Arrested, requiring graduated exercise to qualify for the quiescent and arrested stages, we have but little time to discuss. We believe, however, that such strenuous exercise at the time advised most unwise, especially the month of a half hour's walking exercise twice daily by the active cases to qualify for the quiescent stage. It should be noted that, according to the classification, this exercise may begin one month after the constitutional symptoms have disappeared.

We doubt very much that graduated exercise should be used for the determination of activity, but should be deferred to the time when the chances for doing harm are at a minimum, that is, when the lesions seem healed. Graduated exercise may than be safely used for hardening purposes.

It is well here to summarize the status of cases qualifying for the arrested stage as provided by the criteria of the National Classification. Most of them will have only improved lesions, there will be no uniformity as to the type or extent of lesion present, and many on discharge will develop new activity and a high percentage will die of pulmonary tuberculosis within a certain period.

The above seems to us a bad situation but may be greatly remedied provided the National Classification be slightly changed, and provided physicians will treat patients until arrest occurs by the proposed criteria. If specification no. 3 under Arrested, "X-ray findings compatible with a stationary or retrogressive lesion," were replaced by "X-ray findings compatible with a radiographically healed lesion," the status of our cases coming to arrest would be greatly changed for the better.[4]

[4] The National Classification with the changes proposed would not be suitable for cases which had had chest surgery, such as pneumothorax or thoracoplasty. It would seem that these should have a separate classification adapted for surgical cases only, such as suggested by the Municipal Sanitarium of Chicago.

Having had on the average from ten to twelve months longer treatment, and with lesions that have become radiographically stationary, hard and clear cut, a status which is more or less a definite anatomical entity will have been reached, and on discharge reactivations will be at a minimum and mortality almost nil.

DISCUSSION

The National Classification only recognizes activity in pulmonary tuberculosis to be a constitutional manifestation. It would seem that a lesion which is showing either progression or retrogression as seen by serial roentgenograms should also be considered as having manifestations of active disease. Some regard changes in roentgenograms as evidence of pathological activity, but do not admit that progressive disease as shown in the comparison of roentgenograms is active disease. We do not understand such a distinction, but believe that the changes in tuberculous lesions demonstrable roentgenologically are a most important sign of activity, and especially so because they may be seen in most cases long after the constitutional symptoms have disappeared. Furthermore, we have shown that it is not safe to treat pulmonary tuberculosis with the idea that when the constitutional symptoms have disappeared the patient is well on toward recovery and within six or eight months of arrest. A much safer way is to consider a patient in whom the constitutional symptoms have disappeared to have entered a phase in his treatment when he may begin to improve by prolonged rest in bed. The case should still be considered active and rest should be continued until the radiographs show no more changes and their character points to a radiographically healed lesion.

Opposed to this view is the idea held by some that it takes too long to attain a radiographically healed lesion. Cases are cited where serial roentgenograms have shown changes progressive or retrogressive for five, six, or seven years or more. On inquiry it was found that many of these patients had not been resting, but were undergoing exercise, some carrying on their old jobs. Under such conditions we cannot expect rapid clearing and healing of tuberculous lesions. Attention is again called to the fact that the average time to attain a radiographically healed lesion in our hundred cases under conditions of rest was two years, while 89 per cent attained healed lesions within three years.

It would seem much better to spend a little more time, from ten to

twelve months more, to attain a healed lesion with a posthospitalization mortality of 0.6 per cent than to discharge patients with retrogressive lesions and with a mortality ranging from 13 per cent to 20 per cent and more.

Let us repeat again what is meant by a radiographically healed lesion. As stated above, a lesion is so considered when serial roentgenograms show the shadows to be stationary in appearance and with clear-cut margins. Any shadow changing in size or density and having a peripheral faint density is not the shadow of a healed lesion, as the peripheral reaction indicates active infiltration. This radiographic interpretation should be the final factor in the determination of arrest, and the anatomical state which it indicates is reached many months after the constitutional symptoms have disappeared and the sputum has become negative. Although we consider this criterion for arrest a great step forward, it is not 100 per cent perfect. It is not safe to consider lesions with massive fibrosis as healed until many months of observation have passed. Lesions may be concealed behind the heart, mediastinum, or diaphragm. It may sometimes occur that radiographically healed lesions are not found anatomically healed at autopsy, as X-ray apparatus and technique have not as yet been so perfected that all areas of calcification and ceaseation will cast shadows on the X-ray film. Again, the interpretation of the X-ray film is a factor of great importance. We have seen phthisiologists and even roentgenologists differ greatly in their radiographic interpretation of a healed lesion. It is quite evident that such differences in interpretation would mislead in our expectations of the autopsy findings of the cases in question.

Some are inclined to doubt the validity of a negative X-ray in the presence of râles. To us, Brun's article on *Parenchymal Râles in Pulmonary Tuberculosis*, published in 1925, gives the only plausible explanation of the mechanism of production of the type of râles most often heard in pulmonary tuberculosis, the medium sized râles which occur in showers on inspiration following an expiratory cough. After extensive examination of lungs at autopsy over areas where these râles were heard, Bruns found no moisture. He came to the conclusion that these râles are atelectatic in character, the showers of râles being caused by the sudden expansion of partially or completely collapsed pulmonary lobules.

Once the above theory of râles is adopted, we need to worry no more

if râles are present or absent with negative serial roentgenograms. Personally we pay very little attention to râles when serial roentgenograms show a stationary, hard, clear-cut lesion.

It has been our custom for the past thirteen years to observe the resolution and retrogression of tuberculous lesions, checking up frequently with roentgenograms. Many cases have come to autopsy, and we have been impressed with the accuracy with which the pathological findings have been portrayed by the X-ray. Unfortunately we have not had the opportunity to observe the autopsy findings of many patients who have died with lesions that appeared radiographically healed.

We report one case:

C.R.: Male, white, born January 14, 1892. Admitted to Veterans' Hospital, Livermore, California, March 12, 1929. Reported to have had two haemorrhages while in the Army in 1917. Discharged from Army "condition good." Has not felt well since discharge and has worked only half of the time. A diagnosis of pulmonary tuberculosis was made about one month before entrance to the hospital. On admission, patient complained of loss of strength, slight cough, slight expectoration and loss of weight. Physical examination showed medium sized râles from the right second rib and fourth dorsal spine up, and from the left fifth rib and third dorsal spine up. These râles were heard only on inspiration followed by an expiratory cough. Patient's sputum showed no tubercle bacilli after repeated examinations. His temperature ranged from 36.8° to 37°C., pulse from 70 to 80. The radiograph showed a somewhat discrete productive lesion extending from the fourth rib to the apex in both lungs, with a circular shadow suggestive of a cavity in the apex of the left lung. Radiographs were taken at frequent intervals and showed continuous retrogression of the lesions without interruption for one year. Radiographs taken April 30, 1930, compared with those taken on entrance showed marked general clearing throughout the right and left upper lobes, especially in the right apex and opposite the first and second interspaces. The area reported as suggestive of cavity had disappeared. A radiograph taken November 24, 1930, and compared with one taken August 19, 1930, showed a slight increase of infiltration second rib up on the right. On June 8, 1931, patient left the hospital "against medical advice." He was still considered active at that time. He again entered the hospital September 18, 1931. Comparison of radiographs taken showed that the lesion had shown retrogression in the right lung during his stay away from the hospital. His progress was uneventful until he developed appendicitis about November 3, 1932. Patient was operated upon and died November 17, 1932. No radiographic changes were seen in the serial roentgenogram after May 2, 1932, and radiographs taken shortly before the operation showed a fairly hard lesion or one that we

considered on the verge of being compatible with a radiographically healed lesion.

Autopsy: (Lungs only.) Right lung was free except over apex where several firm adhesions were present. The apex had numerous emphysematous blebs. Cut section revealed moderate fibrosis in the apex. Left lung was adherent over the apex which had numerous emphysematous blebs. Cut section showed moderate fibrosis in the apex and marked congestion over the rest of the lung.

Comment: It is to be noted that although careful search was made, no macroscopical residues were found except the fibrosis. No areas of infiltration, caseation, or calcification were noted.

The above is but one case and proves little, but it may possibly suggest that if X-ray films are properly interpreted, there may not be a great difference, even at this time, between the radiographically healed lesions and autopsy findings.

That the mortality rate of the 156 cases cited above, discharged with what we considered radiographically healed lesions, was but 0.6 per cent, suggests that the pathological residues, if present and which may not have been detected radiographically, were not sufficient to interfere materially with the carrying on of an active life.

SUMMARY

A questionnaire sent to a representative group of sanatoria reveals the following:

1. The X-ray is the most important criterion for the determination of arrest and discharge.

2. While 32 per cent believed that the radiographic criterion of arrest should be a healed lesion, 44 per cent accepted the specification as outlined by the National Classification, "a retrogressive or improving lesion." In regard to discharge, while 26 per cent believed only in discharging their patients when the lesion appeared to be healed, 50 per cent believed discharge was indicated when the lesions were retrogressing.

3. Statistics were presented of nearly 1,900 cases showing the following after-results of treatment:

a. Of 1,771 cases discharged with retrogressive or improved lesions, and classified as quiescent and apparently arrested, 359, or 20 per cent, died.

b. Of 874 cases discharged with retrogressive lesions, and classified as apparently arrested, 121, or 13.8 per cent, died.

c. Of 156 cases discharged with lesions which appeared to be healed radiographically, 1, or 0.6 per cent, died.

4. The above seems to indicate that the nearer a patient's condition approaches the status of what we call a radiographically healed lesion, the fewer posthospitalization reactivations and deaths occur.

5. It would seem, therefore, that we may save many lives if the X-ray specification for arrest in the National Classification, "a stationary or retrogressive lesion," were replaced by "a radiographically healed lesion."

6. A case is reported of a patient who was about to be discharged with a lesion which appeared to be radiographically healed. A necropsy performed after his death from appendicitis showed the lesion to be anatomically healed as seen macroscopically.

7. The anatomical status of a case with lesions which appear radiographically healed is discussed. It is granted that a radiographically healed lesion may in a comparatively small percentage of cases not mean an anatomically healed lesion. It has been shown, however, that the posthospitalization reactivations and deaths of patients having what appear to be radiographically healed lesions are cut to 0.6 per cent.

8. With the rapid improvement of X-ray apparatus and technique, the time is rapidly approaching when the term "a radiographically healed lesion" will still more nearly approach the status of the anatomically healed lesion.

9. Before the X-ray came into use, symptoms were the guide for the treatment of pulmonary tuberculosis. Unfortunately many still follow this rule and ignore the roentgenographic findings, not seeming to realize that when the symptoms disappear the lesions often remain much the same. The National Classification is based largely on this misconception.

We wish to express our sincere appreciation to Dr. Frank E. Brewer, the Manager of this Facility, who assisted us greatly in the gathering of the statistics which were used in writing this paper.

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LOWER LOBE TUBERCULOSIS[1]

WILLIAM H. WEIDMAN AND HUGH B. CAMPBELL

In reviewing the literature on lower lobe tuberculosis one is impressed with the relatively few articles on this subject and the diversity of ideas expressed by them. As early as 1886 Kidd (1) admitted that a basilar lesion was rare, but that the apex of the lower lobe was "very prone to disease and may be attacked before the upper lobe." In 1888, Fowler (2) stated "the upper and posterior part of the lower lobe is a spot only second in point of vulnerability to the apex itself." Apparently these opinions were either disregarded or ignored, for practically all textbooks dealing with pulmonary tuberculosis led the uninitiated to believe that pulmonary tuberculosis originated and remained for the most part in the apices of the lungs. Of course it was known that the lower lobe became affected but it was considered to be an extension of the process downward. It was considered practically impossible that exudative lesions could originate in the lower lobe and spread upward.

With the more prevalent use of the X-ray in the diagnosis of pulmonary tuberculosis it became evident that quite frequently clinically active tuberculosis originated below the apex. Wessler (3) in 1923 described the appearance and diagnosis of these lesions. Assmann (4) in the same year stated that these early lesions can only exceptionally be demonstrated with the aid of physical signs, but these lesions are usually found on the X-ray film to be located below the clavicle, in what he designated as the infraclavicular or subapical position.

Once the tradition of the apical origin of pulmonary tuberculosis was questioned, the proof of the lower lobe origin of tuberculosis was made possible. However, physicians were slow to recognize this possibility. Presumably, this delay occurred because of the faulty interpretation of the X-ray film. Lesions occurring in the middle and lower third of the lung fields were interpreted as arising from the hilum, when in reality quite frequently they occupied the posterior portion of the lung. Consequently, when viewed in the posteroanterior position, it was understandable how the misinterpretation occurred, because there was a

[1] From Uncas-on-Thames, Norwich State Tuberculosis Sanatorium, Norwich, Connecticut.

superimposition of the hilum image on the lesion itself. Pathologists claimed, and justly so, that interpretations of the X-ray films were faulty, for quite frequently cavity formation was noted in the position of the lower lobe without any demonstrable evidence of cavity formation near the hilum. Sweany, Cook and Kegerreis (5) in the study of the position of the primary cavitation in pulmonary tuberculosis demonstrated that the apices of the lower lobes not infrequently contained the oldest lesion in the anatomical specimen. With the more general use of the lateral position in X-ray examination and frequent resourse to fluoroscopy, confirmation of the pathological findings has been made. The importance of the lateral film has, as yet, not been sufficiently stressed.

The X-ray films of all patients admitted to this institution from January, 1932, until October, 1936, have been reviewed. An attempt has been made to select only those cases which have a definite lower lobe lesion. It is true that some of the cases included in this series have lesions in other portions of the lung field other than at the base. It was felt that these lesions represented daughter-foci from the original basilar lesion or that the basilar lesion was a pneumonic or bronchopneumonic infiltration resulting from a previous infection from some other site in the pulmonary parenchyma, for it is not our contention that these lower lobe lesions represent a primary infection. The cases have been grouped as basilar really because the predominating lesion is situated in the lower lobe. All cases have been excluded in which any doubt could be expressed as to the location of the predominating lesion. In this discussion we do not wish to express an opinion as to the origin or mode of the development of these lesions, for frankly we do not know. This matter will be discussed more fully later.

The female and male patients have been separated for obvious reasons to be subsequently shown. The nontuberculous patients, those with bone tuberculosis, those admitted directly to the Surgical Department from other Sanatoria, and readmissions have been excluded. Of the remaining group 677 females were definitely proved cases of pulmonary tuberculosis, 29 of whom had lower lobe lesions. Of the males, 724 had pulmonary tuberculosis; 11 of these are included in our series (table 1).

Dunham and Norton (6) in 1927 found over a two-year period 26 cases in a 250-bed hospital, Ross (7) in 1930 found 11 in 60 tuberculous nurses, Lathrop and Lyman (8) 88 cases in 2,809 patients with tuber-

culosis, and Hamilton and Fredd (9) 10 in 349 cases in a one and one-half year period. Reisner (10), in a more comprehensive study, found 34 cases of whom 24 were women and 10 men, and of whom 24 were white and 10 Negroes. Thirty-one of the 34 were selected from 4,494 patients admitted over a four-year period (of whom three quarters were male, and one quarter female). Dunham found a preponderance of lower lobe tuberculosis in the negro race. In our series of 40, but one case was colored. The age group is as follows: female, 15 to 20: 8 cases, 21 to

TABLE 1

Characteristics of lower lobe tuberculosis

	MALE	FEMALE
Total number of cases of pulmonary tuberculosis	724	677
Total number of cases of lower lobe tuberculosis	11	29
Percentage of lower lobe tuberculosis	1.52	4.27
Side involved:		
Right	7	21
Left	4	8
Cavity:		
Present	6	17
Questionable	2	4
None	3	8
Onset:		
Acute	4	17
Gradual	7	12
Sputum:		
Positive	9	23
Negative	2	6
Bronchiectatic changes	0	2
Spread during treatment	5	14

25; 9 cases, 26 to 30; 6 cases, over 31; 6, the oldest being 39; male, 14 to 20: 5, 21 to 27; 4, over 30; 2, the oldest being 38. Reisner found that two-thirds of his cases were between the ages of 17 and 30. In the fifth decade he found one; in the sixth decade, 2, one of the latter being a tuberculosilicotic.

The chief difficulty encountered in determining the exact origin and incidence of lower lobe tuberculosis is that the infection generally spreads completely throughout both lung fields before death. In two of our

cases, extensive apical caviation developed before death, overshadowing the lower lobe lesion. As a matter of fact, roentgenologically the latter would have been entirely overlooked, had not previous X-ray examination been made. The fact that Ross found eleven lower lobe lesions in sixty tuberculous nurses probably indicates that these lesions are an early manifestation of clinically active pulmonary tuberculosis. The inference is, of course, that nurses would be more likely to have an early diagnosis made than the ordinary lay person. To some writers this is a distinct type of tuberculosis which exhibits certain similarities with the childhood forms, Pindell (11). They feel that it is an extension from the hilum, either by contiguity to tracheobronchial lymph nodes or by perforation of a caseated node into the bronchus. Others feel that it is but a retrograde lymphatic extension. However, Pancoast, in the discussion of Dunham and Norton's series, felt that it is an atypical manifestation of miliary tuberculosis due to a blood-stream infection.

Fishberg (12) does not classify lower lober tuberculosis as a separate entity, but mentions under the discussion of infraclavicular infiltrations "the patch is found most commonly on a level with the third or fourth rib near the axillary portion of the lung; exceptionally it may be detected in any other part of the lung field, even in the lower lobe." His diagram demonstrating this fact (page 453) shows in the posteroanterior film a cavity situated in the right hilum. Dunham and Norton feel that these lesions are peculiar to juveniles, and have demonstrated by necropsy many primary foci situated elsewhere in the body such as the kidney, bone, etc. Our feeling is, from this group of cases, that lower lobe tuberculosis is usually of the reinfection type and could with entire justification be included under the infraclavicular variety. With the existing limitations of X-ray examination a definite opinion as to the presence or absence of an early focus is not warranted. In some instances this is so obvious as to defy being overlooked, but frequently necropsy reveals foci which are not visible in the roentgenogram.

The onset is usually acute. Owing to the difficulty encountered in obtaining accurate histories, a definite conclusion cannot be drawn from this series. Quite frequently, patients may have slight prodromal symptoms which may be ignored. They suddenly become ill with a cold, grippe or pneumonia-like illness. Seventeen of the 29 female patients had a definitely acute onset, the remainder being classified as gradual. Four of the 11 males had an acute onset.

We feel that the early cases included in this series were diagnosed early chiefly because others in the family had had tuberculosis and that, as soon as cough and other symptoms of tuberculosis became manifest, their interest was aroused.

Lawrason Brown (13) feels that lower lobe tuberculosis does occur, but is so rare that a diagnosis is not justified from the roentgenogram alone, nor is it justified from any method of examination unless tubercle bacilli are found in the sputum. When one considers that the presence of 100,000 tubercle bacilli per 1 cc. is necessary for a definite bacterioscopic diagnosis by simple smear, and that according to Woolley (14) 5,000 tubercle bacilli per 1 cc. must be present in the sputum if they are to be found by concentration methods, it seems unlikely that an early diagnosis can be made by depending entirely upon a sputum examination. While waiting for a growth to appear on a culture or for tuberculosis to develop in an infected guinea pig, valuable time may be lost. These procedures are not discredited. They have been and should be employed, but dependence upon a laboratory diagnosis has been overemphasized by some writers. We do not feel that it is necessary to delay the diagnosis for bacteriological confirmation if particular attention has been paid to the history of contact, the personal history and a proper X-ray examination. Twenty-three of the females had positive and 9 had negative sputa. One of the latter died and a necropsy revealed pulmonary tuberculosis. Eight of the males had positive and 2 had negative sputa.

Unfortunately a definite statement as to the prevalence of fever cannot be made because of the frequently delayed entrance into the sanatorium. The majority of patients manifest a temperature of 99°F. or higher. However, one is impressed with the degree of progression in certain cases without manifest clinical signs and symptoms. Quite frequently there is little if any reaction until the lesion has assumed extensive proportions (plate 1, figure 5). It is in this type of case that such laboratory procedures as the sedimentation rate and Medlar's index are valuable in determining the activity of the process.

Cases unresponsive to the available therapeutic measures run a progressive and rapidly downward course with concomitant fever. The usual secondary involvements of larynx and intestines occur.

Frequently lower lobe tuberculosis is diagnosed as unresolved pneumonia and the proper medical attention is delayed. Four of the 40

cases were at one time diagnosed as pneumonia. We feel that the incidence of this is actually much higher. Haemoptysis of one dram or more occurred in 13 of these patients.

The physical findings are usually prominent in the far advanced cases, although quite frequently difficulty is encountered in diagnosing cavity formation. In the early cases and, in fact, in a few of the advanced cases physical signs are entirely absent.

A few months ago, while reviewing paper films in the Connecticut State College, a girl, 18 years of age, was found to have a large cavity in the right lower lobe with a small infiltration in the contralateral lung. Stereoscopic examination was advised. (Plate 1, figure 5.) The apparent absence of all physical findings, in the face of a cavity demonstrable by X-ray, was not only impressive, but disconcerting. Furthermore, it was impossible to elicit any definite history of illness other than slight morning cough and a feeling of tiredness.

PLATE 1

FIG. 1. Case 1 (female, 39). August 31, 1935. Large cavity in subapical region of the right lower lobe with an infiltration issuing from the left hilum.

FIG. 2. Case 1. October 16, 1935. One and one-half months later. Cavity obliterated, sputum negative. Patient remained on strict bed-rest; no collapse therapy employed.

FIG. 3. Case 2 (female, 47). August 17, 1936. Infiltration issuing from left hilum; diagnosis influenzal pneumonitis.

FIG. 4. Case 2. September 11, 1936. Four weeks later. Clearing of infiltration.

FIG. 5. Case 3 (female, 18). Cavity in left lower lobe and infiltration in contralateral lung. Case discovered in routine X-ray examination of Connecticut State College Freshmen. No complaints except tiredness.

In some cases in which unfortunately the sputum examination is frequently negative, positive signs are almost consistently absent. In this group a positive diagnosis seems warranted on the X-ray evidence and history alone. They should be treated as tuberculous patients without waiting for the appearance of a positive sputum.

It is generally conceded that in the X-ray diagnosis one must exclude unresolved pneumonia, chronic pneumonitis, haemorrhage, bronchiectasis, abscess and lung tumor when the lesion is situated in the lower lobe. However, in the literature reviewed the influenzal type of pneumonitis has not been included. We feel that this is very important in the differential diagnosis. It is characterized by an acute onset. There is usually a temperature of 100°F., with general malaise, cough and headache. The condition has not been recognized roentgenologically

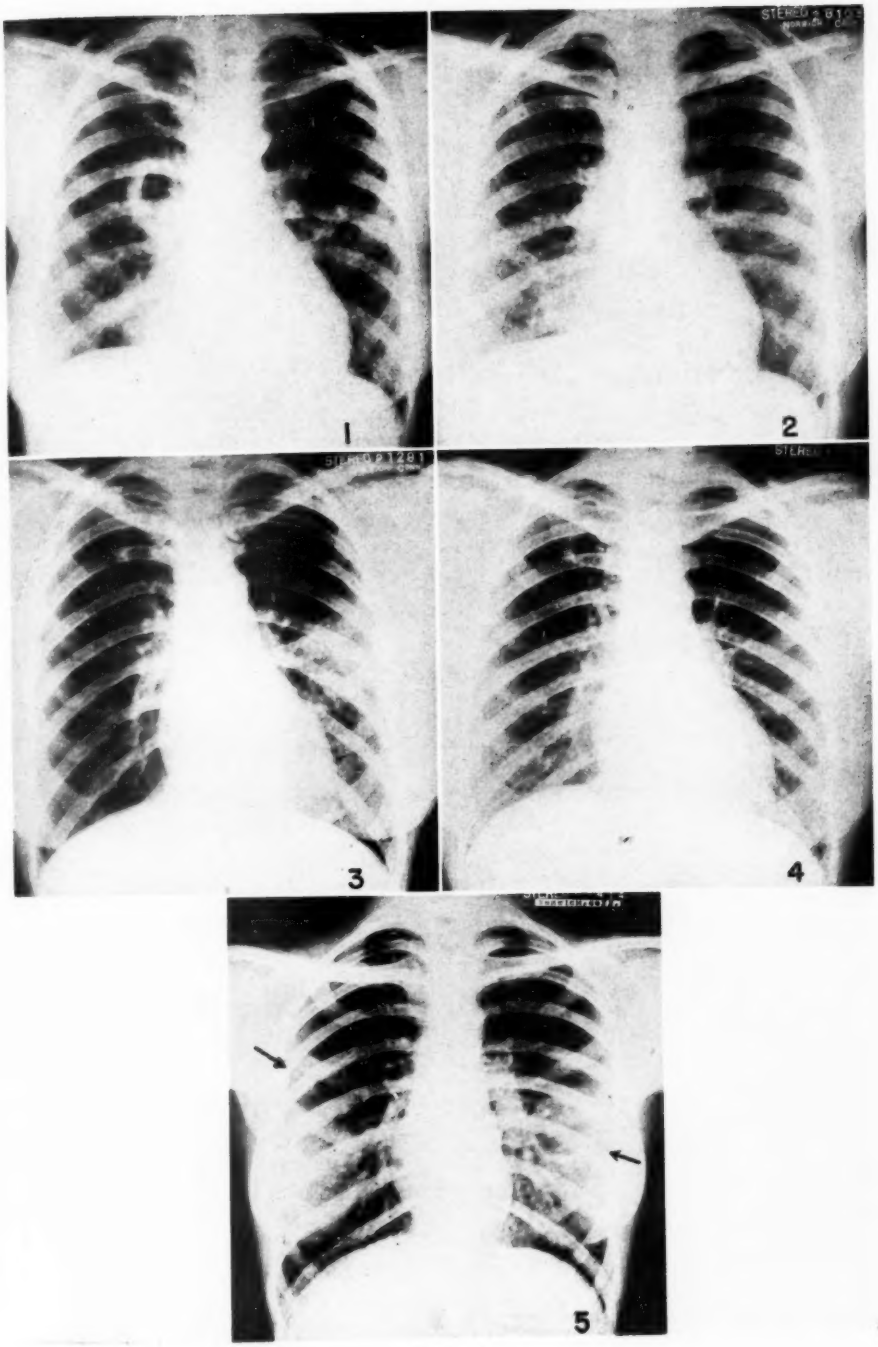

PLATE 1

until fairly recently. The lesion shows a hazy bronchopneumonic infiltration situated in the middle or lower third of the lung field. It clears rapidly in from 7 to 10 days and leaves no residual roentgenological abnormalities (plate 1, figures 3 & 4).

In lower lobe tuberculosis there is either an acino-nodular infiltration issuing from the hilum or a homogeneous density which quite frequently has a central area of rarefaction. It is in proximity to the hilum and is at or below the middle third of the lung. This latter picture can quite easily be mistaken for lung abscess. One is impressed with the rapidity of development and size of the cavity formation. Frequently the cavities are thin-walled with relatively little or no surrounding inflammatory reaction (plate 1, figure 5). Of course, owing to the situation of the cavities, they probably appear larger than they actually

PLATE 2

FIG. 1. Case 4 (female, 16). October 5, 1933. First admission.

FIG. 2. Case 4. January 22, 1935. Second admission. Cavity in the left lower lobe, with an infiltration in the contralateral upper and lower lobes.

FIG. 3. Case 4. February 16, 1935.

FIG. 4. Case 4. February 20, 1935. Pneumothorax instituted January 29, 1935, two and one-half weeks previously. Cavity prominent in the left lower lobe.

FIG. 5. Case 4. April 7, 1936. Left lung completely reëxpanded. Pneumothorax discontinued May 23, 1935, after five months' time. A left temporary phrenic nerve paralysis substituted because of tachycardia. Lysholm grid used to show the lesion posterior to the heart. The left diaphragm is still slightly elevated.

FIG. 6. Case 4. September 1, 1936. Reappearance of the infiltration in the right lower lobe and a new infiltration in the left upper lobe.

are. In ordinary examination in the posteroanterior position the cavity, being situated posteriorly in the lung, is at a maximum distance from the X-ray film. Consequently, the actual size is smaller than the apparent size.

In the female patients cavity formation was present in 17, questionable in 4 and absent in 8. In the males, 6 showed cavity formation, in 2 it was questionable and 3 showed none. Almost invariably the cavity is situated in the apical or subapical portion of the lower lobe. Every patient with a lower lobe lesion should be X-rayed in the lateral position and a complete fluoroscopic study should be made so that a definite topographical diagnosis can be made. Occasionally, as in one of the series, the lesion is situated posterior to the heart (plate 2, figures 1 & 6). This girl was first admitted in October, 1933, and remained

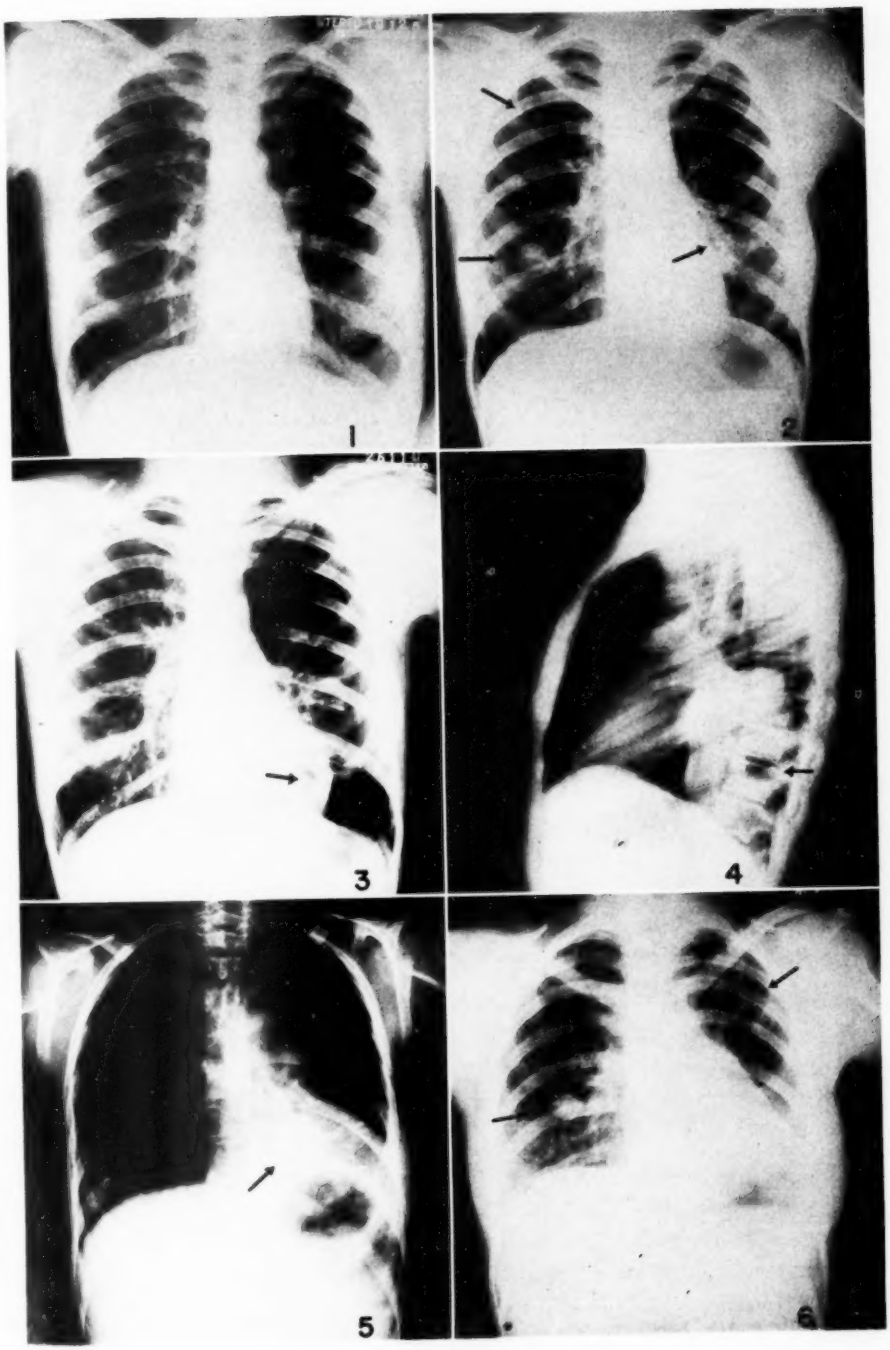

PLATE 2

here until August, 1934. Her chief complaints on admission were a slight cough, an occasional chill and a small haemoptysis. Previous to her first admission in September, 1932, she complained of recurrent attacks of dyspnoea. The following December she became acutely ill and a diagnosis of asthma and pneumonia was made at the Hartford Hospital. In May, 1933, there was a recurrence of dyspnoea with pain in the chest. In August, cough with questionable expectoration developed. On admission she showed rhonchi in the lower half of both lungs. Her temperature was 99°F. and her pulse was rapid. An X-ray film at another sanatorium did not show any sign of pulmonary tuberculosis. The admission X-ray film showed a thickened apical pleura with intensification of the basilar trunks, particularly the left. After discharge the patient remained at home. She was readmitted in January, 1935, with a positive sputum. There was X-ray evidence of infiltration and cavity formation situated at the left cardiac border with evidence of a new infiltration in the right lung, in both upper and lower lobes.

Although this patient on the first admission was treated essentially as one with pulmonary tuberculosis, we feel from the X-ray evidence that insufficient studies were made on her. The question arises whether this patient should have received a lipiodol injection for delineation of the lower lobe bronchi. Two of the female patients included in this series showed, after lipiodol injection, bronchiectatic changes, presumably resulting from tuberculosis. This fact raises some interesting questions. Is this condition usual in lower lesions and, if so, is it a cause for the difficulty encountered in the treatment? Unfortunately bronchography is not warranted in all these cases, for even though some writers claim that iodized oil can be administered with impunity a number of unfavorable reactions have resulted.

Another interesting fact is the preponderance of the involvement of the right lower lobe. Twenty-one of the female patients showed a right lower lobe lesion and in only 8 was the left lower lobe involved. Seven of the males had lesions situated in the right lower lobe and 4 in the left lower lobe. An explanation of this phenomenon has been advanced by Reisner on a purely anatomical basis. He thinks that it is chiefly due to a relatively inactive and less aerated pulmonary parenchyma.

Lower lobe lesions are characterized roentgenologically by an apparent instability and variability of the process. They either advance rapidly or clear rapidly. Spreads are frequent. Fourteen of the females showed

new lesions in some other portion of the lung field. In five of the men spreads occurred during treatment. There seems to be a preference for the subclavicular area in the homo- or contralateral lung or for the contralateral base (plate 2, figure 2).

Pindell in 1933 stated, "basilar lesions are treacherous." Dunham in 1927 stated, "a basilar lesion is a very virulent type of infection more prominent in the negro and they may be almost uniformly fatal." Of course, his was an essentially juvenile study. In his fatal cases exhaustive necropsy studies were made in an attempt to discover extrapulmonary foci. Dunham reached the conclusion that the majority of the patients showed a primary focus in the bones, kidneys, etc. Believing that lower lobe tuberculosis was a result of a generalized tuberculosis, Colton (15) in 1928 stated, "the prognosis is grave." Reisner in 1935, however, pointed out that, inasmuch as the majority of these cases are of the caseocavernous type, the prognosis is not particularly different from similar lesions in the apex. From our studies we would conclude that the prognosis is determined not only by the type and character of the infiltration, but also by its situation and the difficulty encountered in producing an effective collapse of the diseased lung, particularly in the presence of cavities. This is primarily the result of either preexisting adhesions or the development of adhesions subsequent to fluid formation. All too frequently, before the homolateral lesion is under control, a new infiltration develops in the contralateral lung. It is true that occasionally one sees an apparently spontaneous obliteration of a cavity, as evidenced by one patient in this series (plate 1, figures 1 & 2). This is considered to be an exception. Cases without demonstrable cavitation and of the acino-nodular type represent probably the early state of this disease. The lesions of the caseocavernous type are very unstable.

In considering the foregoing characteristics of lower lobe tuberculosis an attempt has been made to formulate a reasonable method of therapy. But before discussing treatment a brief outline of the results obtained will be presented (table 2). Five of the females were treated by bed-rest alone; one of these, remaining but a short time, should be classified as untreated. Three satisfactory results were obtained; 1 died. Of the 3 with satisfactory results, 2 were of the acino-nodular type without positive sputum or demonstrable cavity; the other showed definite cavity formation with positive sputum. Actually, the fatal case should not be classified from our admission X-ray film as a basilar lesion, for

at that time an exudative lesion without cavity formation was uniformly distributed throughout both lung fields. However, the early films loaned to us by Undercliff Sanatorium were very interesting. They showed a small mottled infiltration in the left lower lobe which spread to the right base and then to the upper lobes. In view of a persistently negative sputum a diagnosis of mycotic infection was entertained at

TABLE 2*

Results of treatment

PHRENIC NERVE INTERRUPTION	NUMBER TREATED	RESULTS		
		Satisfactory	Partially satisfactory	Unsatisfactory
Permanent, initial	4(1)			4(1)
Permanent, after failure to obtain free pleural space	3(1)	(1)	1	1
Permanent, after unsuccessful pneumothorax	1		(1)	
Temporary, after unsuccessful pneumothorax	2			2
Permanent, supplementing pneumothorax	2	2		
Temporary, supplementing pneumothorax	1		1	
Pneumothorax				
Pneumothorax alone	15(5)	6(4)	6(1)	3
Pneumothorax with permanent phrenicectomy	2	2		
Pneumothorax with temporary phrenic nerve interruption	3		2	1
Pneumothorax after failure of permanent phrenicectomy	2	1		1
Bed-rest alone, no collapse therapy	6(2)	4(1)	(1)	2
Cases not treated	1			
Cases too early for classification	5(1)			
Thoracoplasty after failure of phrenicectomy and pneumothorax	1	1		

* The figures without parentheses indicate the total number of patients in each group; the figures in parentheses indicate the number of male patients.

the onset. The existence of diabetes mellitus complicated the picture. The sputum remained negative but necropsy revealed a far-advanced pulmonary tuberculosis. Four cases receiving pneumothorax treatment for 10 months or less have been observed too briefly for any conclusions. Of the patients treated by phrenic nerve paralysis, 3 received a permanent phrenicectomy as an initial measure and failed to improve, so

that pneumothorax was later instituted. Of 2 with phrenicectomy following failure to administer pneumothorax, one failed to improve and one showed unfavorable changes after four years. Two temporary nerve paralyses after unsuccessful pneumothorax administration proved unsatisfactory; two phrenicectomies supplementing pneumothorax treatment proved beneficial. One temporary phrenic nerve interruption, supplementing pneumothorax, is classified as partially satisfactory. In one patient in whom phrenicectomy and pneumothorax both failed to halt the progression of the lesion, a thoracoplasty has been done. It is too early to state the outcome of this procedure. It is interesting to note that this case showed bronchiectatic changes at the left base demonstrated by lipiodol injection.

Of the patients receiving pneumothorax treatment, ten receiving pneumothorax alone, two results were satisfactory, five partially satisfactory and three unsatisfactory. In most of the patients classified as partially satisfactory either insufficient time has elapsed or, as in one case, there is an occasional positive sputum. In two cases, pneumothorax was instituted after phrenic paralysis had failed, one showing satisfactory and one unsatisfactory results. However, in the latter case, a two-year period intervened between the administration of pneumothorax and the time of phrenicectomy.

Three male patients received phrenicectomy; one in whom there was an initial phrenicectomy died; one in whom it was impossible to administer pneumothorax showed improvement after a year's time and is classified as partially satisfactory; one, in whom a phrenicectomy was done because of failure to collapse the lower lobe with pneumothorax, is classified as partially satisfactory.

Of 5 cases receiving initial pneumothorax without other collapse therapy, 4 showed satisfactory results, 1 partially satisfactory. In the one patient classified as partially satisfactory, treatment was given for one year, and the patient was discharged for breach of discipline; his condition at that time was excellent. Of the 2 men receiving bed-rest, one showed satisfactory and the other partially satisfactory results.

In discussing the best form of therapy for these cases it is necessary to determine whether the sputum is positive. From our experience it is found that if the sputum is negative and if there is no demonstrable evidence of cavity formation, and the lesion is of the acino-nodular type with no definite physical findings, strict bed-rest, with frequent, at

least weekly X-ray examination, is probably the most satisfactory form of treatment. In the exudative lesions with a pneumonic or bronchopneumonic type of infiltration with cavity formation, with or without positive sputum, pneumothorax is the method of choice. It is felt that pneumothorax should be administered immediately, for the longer the delay the more likely are adhesions to develop. In the cases without obvious adhesions the upper lobe apparently collapses disproportionately more than the lower lobe. As the treatment is continued the lower lobe is slowly and gradually compressed (plate 3, figure 4). There appears to be a gradual clearing of the lower lobe from the periphery to the central portion. If pneumothorax has been maintained for some time with a consequent resolution of the process, the lower lobe will be compressed disproportionately more than the upper lobe. It is felt

PLATE 3

FIG. 1. Case 5 (female, 37, colored). August 1, 1933. Admission X-ray.

FIG. 2. Case 5. November 10, 1933. Initial permanent phrenicectomy done one week previously.

FIG. 3. Case 5. November 17, 1933. Lateral film shows high diaphragm and probable atelectasis of the right middle lobe.

FIG. 4. Case 5. April 3, 1934. After two months of pneumothorax treatment (instituted February 12, 1934). The right diaphragm is depressed by the intrathoracic pressure. There is a selective collapse of the right lower lobe and pleurisy with effusion on the left.

FIG. 5. Case 5. August 14, 1935. Decrease of the intrathoracic pressure allows the diaphragm to rise. The high diaphragm obscures the lower lobe.

FIG. 6. Case 5. October 2, 1936. Complete reëxpansion of the lung. The diaphragm is at a higher level. On September 18, while attempting to administer pneumothorax, 30 cc. of fluid was aspirated. The first 10 cc. was clear, the remainder sanguineous.

that an effectual collapse is required; that is, a collapse in which the diseased lung is compressed to its utmost. This is in contradistinction to the usual procedure at this institution in the case of a localized apical lesion. In this instance any collapse sufficient to obliterate cavity formation is considered an effectual collapse.

It will be noticed that in a goodly proportion of lower lobe lesions, collapse of cavities is extremely difficult. It is recommended that frequent X-ray studies of the compressed lung be made using the Lysholm grid or an overexposed film. It is thus possible to obtain pertinent information which may be overlooked with the ordinary technique. In those cases in which cavities remain patent or the sputum remains persistently positive further measures are recommended. Taking into

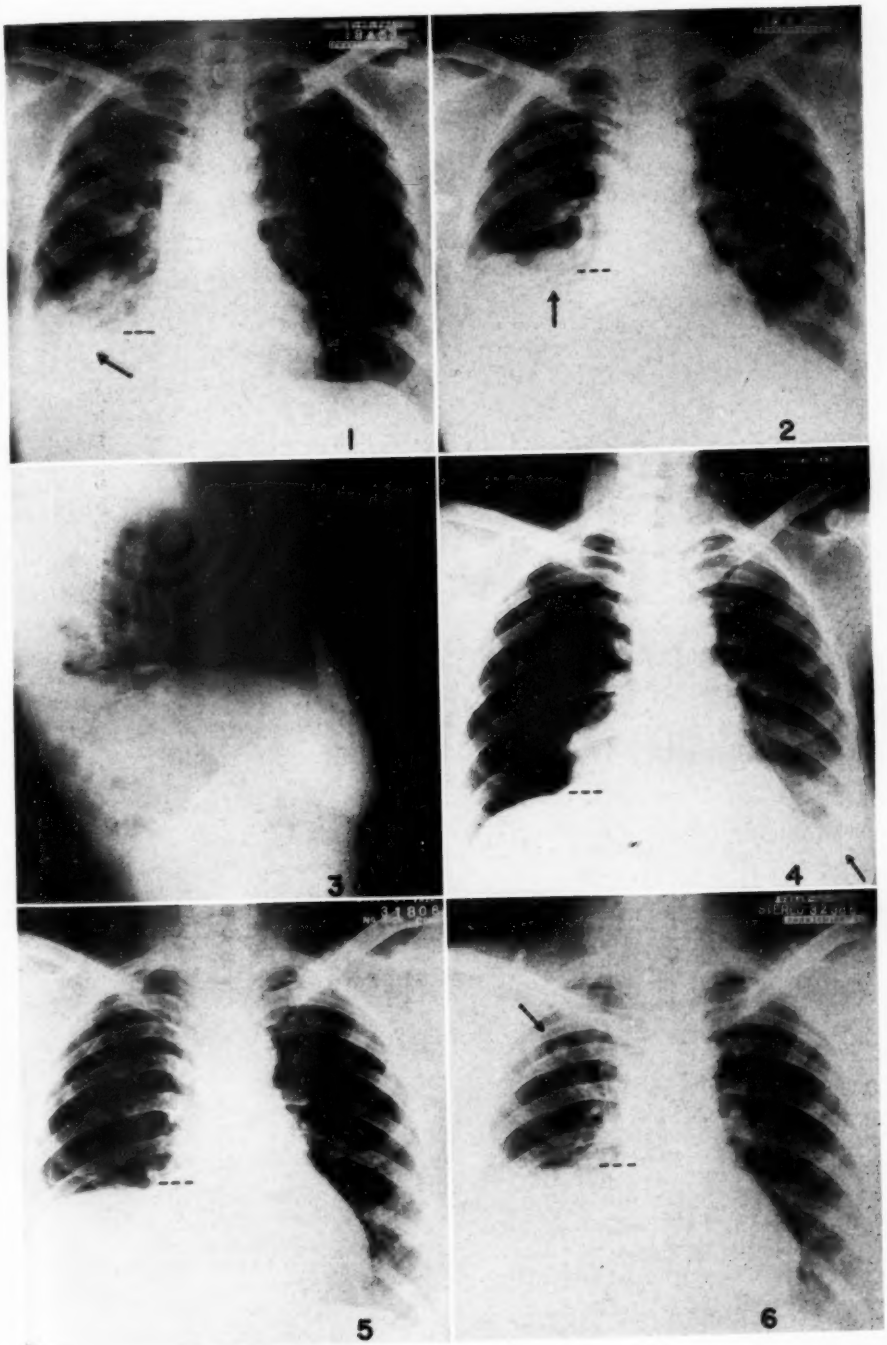

PLATE 3

consideration the usual location of cavities, that is, in the apical or subapical region of the lower lobe, it is easily seen how adhesions can be overlooked, since adhesions may be present along the extreme posterior surface of the lung or on the medial surface of the lower lobe along the posterior sulcus of the thoracic cage. It is quite obvious that on the ordinary posteroanterior film no adhesions will be seen. For that reason, X-ray and fluoroscopic studies in the oblique and lateral positions are indicated.

It is felt that the presence of any adhesions interfering with a satisfactory collapse, irrespective of the presence or absence of tubercle bacilli in the sputum, is an absolute indication for a pneumonolysis. In those cases in which no adhesion can be demonstrated by the ordinary means and the cavity remains patent, it is felt that a thoracoscopic examination is indicated if tubercle bacilli continue to be found in the expectoration. Furthermore, any interfering adhesions should be severed as soon as a diagnosis is made.

In the pneumothoraces complicated by fluid with a subsequent development of diaphragmatic adhesions, a supplementary phrenicectomy seems indicated. However, diaphragmatic adhesions must actually exist. Otherwise either one or two things occur. If sufficient intrathoracic pressure is maintained to produce an effective collapse of the lower lobe, the paralyzed diaphragm is merely depressed. If an insufficient collapse is maintained, the high paralyzed diaphragm, obscuring the lower lobe, not only instills a false sense of security but also makes it impossible to know the condition of the underlying lung (plate 3, figures 1 & 6).

It seems reasonable to state after a study of this series that an initial permanent phrenicectomy is contraindicated. Reisner, discussing this latter measure, states that an initial phrenic neurectomy was done in 8 cases. The cavity was closed in only one instance. In 19 who received pneumothorax 11 showed satisfactory results, one died, one was discontinued because of circulatory embarrassment, and 6 were unsuccessful because the cavities remained patent. In the latter group, he claims that no adhesions were present, yet he fails to state whether the methods recommended above had been carried out, and in none of these was a thoracoscopic examination made.

A word now seems in order as to the completion of treatment. Before these patients are discharged as cured and the treatment terminated, all the available laboratory procedures should be used in an effort to

determine the activity of the lesion. A concentration test of the sputum should be done and the sediment planted on Petroff's media or injected into a guinea pig. The various blood tests, including the sedimentation reaction, should be made. Even then, there will be difficulty in expressing a definite opinion. This comment has recently been made on one of these patients transferred to the State Sanatorium at Shelton, Connecticut, "While Medlar's index and sedimentation rate are active, the appearance of the X-ray and the clinical story indicate satisfactory progress."

Of those pneumothorax patients whose treatments have been terminated, the time elapsed is as follows: 3 years and 3 months; 4 years; 4 years and 7 months; and 1 year and 11 months. In the latter instance doubt has been expressed as to the true condition of the pulmonary lesions. We feel that pneumothorax should be maintained for at least four years in order to make reasonably certain a cure in this type of lesion. None of the patients whose pneumothorax has been terminated for the completion of treatment has received a terminal phrenicectomy. This, however, may be a desirable procedure.

A brief summary of the results obtained is as follows: nine unsatisfactory, eight of whom died; eleven partially satisfactory; fourteen satisfactory to date; five observed too briefly, all improving at present; and one untreated.

It is clearly evident that the results considered in the aggregate are far from brilliant irrespective of the collapse therapy employed. They tend to substantiate the contention that lower lobe tuberculosis is still a definite therapeutic problem.

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THE BRAIN IN CHRONIC TUBERCULOUS MENINGITIS[1]

BERNARD J. ALPERS AND ROBERT A. MATTHEWS

INTRODUCTION

There is abundant evidence that clinical recoveries in cases of tuberculous meningitis may occur in rare instances, and that the incidence of recovery seems to be higher in adults afflicted with the disease than in children. A careful survey of the recorded cases of tuberculous meningitis from 1894 to 1909 by Martin (1) discloses 20 authentic recovered cases, all of which conformed to the strictest diagnostic criteria. Similarly Cramer and Bickel (2) were able to find 45 cases of tuberculous meningitis which had recovered up to 1922. Since then there have been many more recorded instances of recovery in this disease, all of which make it apparent that while tuberculous meningitis is as a rule a fatal disease, it does not always terminate in death, particularly in adults.

It is important to know what changes occur in the brain and meninges in these recovered cases and in cases of chronic tuberculous meningitis. Granted that recovery occurs in some instances, what is the ultimate effect on the cerebral cortex, and what may one expect to find in the meninges? Furthermore, are the changes similar to those found in the typical fatal case of tuberculous meningitis? These problems are important, for if it is true, as some assert, that the meninges are the seat of chronic tuberculous affections not infrequently, it is desirable to know what these changes are both for pathological and clinical reasons. In the following case the opportunity has arisen to study the brain changes in a case of tuberculous meningitis which made a recovery from its acute phase, only to become chronic and terminate fatally six months after the onset of the illness.

CASE REPORT

Acute tuberculous meningitis in a male of 60 with typical features. Guinea-pig test positive. Subsidence of acute signs followed by toxic psychosis and severe deterioration. Progressive weakness and death. Necropsy revealed chronic tuberculous meningitis.

[1] From the Philadelphia Hospital for Mental Diseases and the Laboratory of Neuropathology in the Institute of the Pennsylvania Hospital, Philadelphia, Pennsylvania.

This patient, a man of 60, was admitted to the Philadelphia General Hospital on September 25, 1933, in the care of Dr. S. A. Lowenberg. Since he was stuporous on entrance, only a brief history was obtained from friends who stated that he was unable to leave his bed a week before entrance. For a few days after this he was unable to talk. The day of admission he was found sitting on the toilet seat for three hours and was unable to care for himself.

Examination revealed a stuporous individual who was very emaciated and who had Cheyne-Stokes breathing. The lungs showed signs of consolidation in the right upper lobe, with signs of congestion at the right base. The heart showed evidence of myocardial degeneration. The liver was enlarged. There was evidence of a frank meningitis with a rigid neck and a bilateral Kernig sign.

Laboratory studies revealed 100 to 590 cells in the spinal fluid, lymphocytes predominating by far. The spinal-fluid sugar determined on one occasion was 68 and the chlorides 704. Since the latter was not repeated, it is impossible to draw any conclusions from a single chloride determination taken early in the course of the illness. The colloidal gold was 1,112,321,000. The spinal fluid was examined once for tubercle bacilli but none were found. Guinea-pig injection 9 days after entrance resulted in the death of the guinea pig after 13 days. Necropsy revealed a liver studed with minute nodules which on microscopical examination were found to be typical miliary tubercles. The Wassermann test in the blood and spinal fluid was negative.

The patient was stuporous on admission. With daily lumbar punctures and intravenous glucose his stupor became gradually less pronounced and the signs of meningeal irritation gradually subsided in about 3 weeks. About four weeks after admission he became irritable, aggressive, and very irrational so that transfer to the psychopathic ward became imperative. Here he was mentally confused and gave evidence of severe mental deterioration. His temperature at this time was normal, and he had no evidence of meningeal irritation. He remained quite confused mentally to the end. He was greatly emaciated and never was able to regain his physical strength. He became gradually weaker and died six months after the onset of his symptoms.

Necropsy revealed an old fibrous meningeal thickening at the base of the brain covering most of the basilar structures to the pons. There was an old cystic softening in the inferior portion of the left temporal lobe, the meninges over which were quite thickened. Histological studies revealed a dense fibrosis and a marked infiltration of the meninges with cells of many sorts. The pia-arachnoid was quite fibrotic and was definitely thicker than normal. The infiltrating cells consisted chiefly of lymphocytes and macrophages among which were numerous gitter cells and occasional plasma cells. Fibrosis was quite prominent between the cells. No giant cells were seen, and no vascular changes such as are encountered in acute tuberculous meningitis. In

FIG. 1

FIG. 2

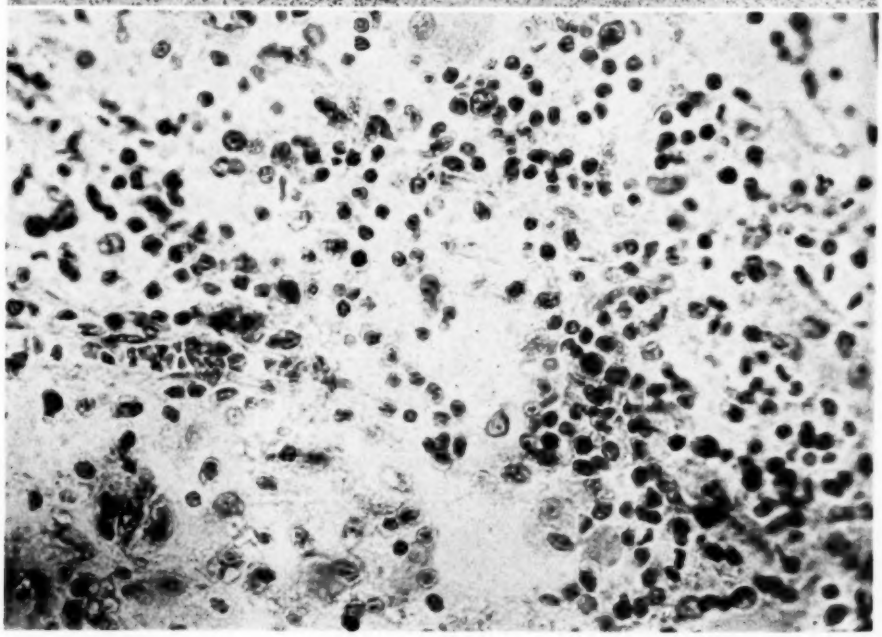

FIG. 1. Extensive infiltration of the meninges with marked fibrosis and hyaline changes in the vessels.

FIG. 2. High power photograph of the cells in the meninges showing the large numbers of small mononuclear cells and large macrophage elements.

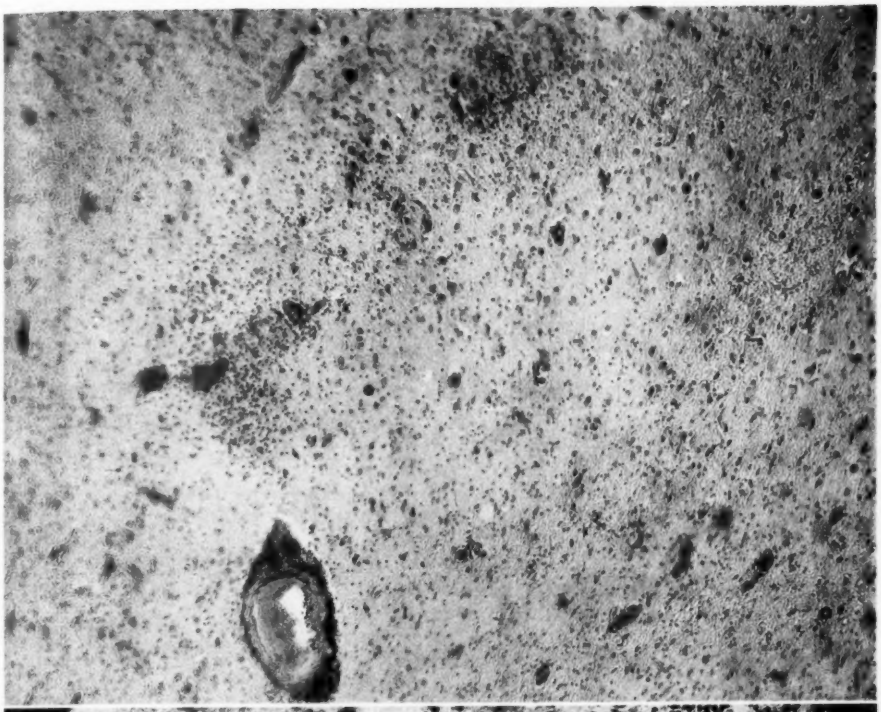

FIG. 3

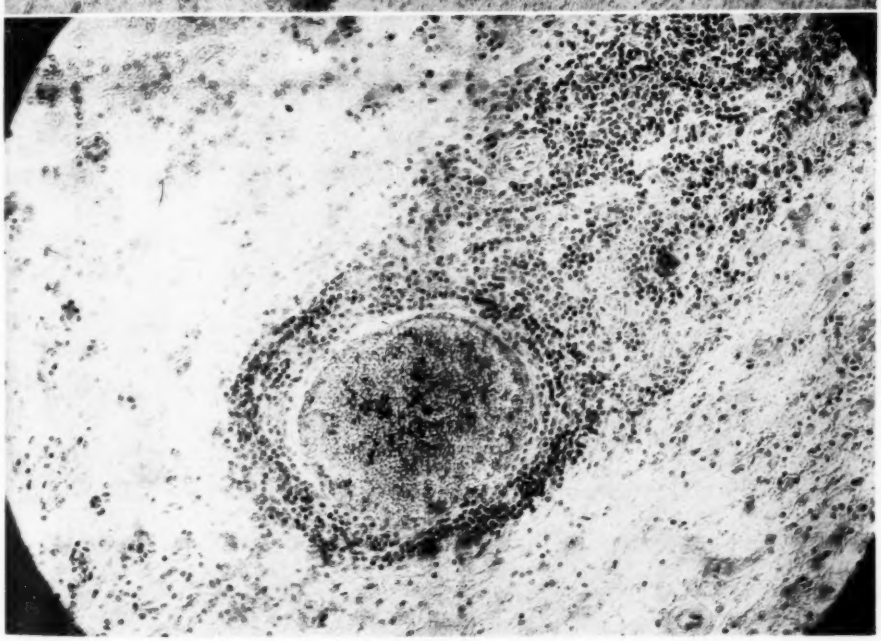

FIG. 4

FIG. 3. An area of cortex showing a vessel with infiltration and a few foci of lymphocytic and glial cells in the cortex.

FIG. 4. A vessel in the cortex showing infiltration of its walls with extension of the process into the surrounding brain tissue.

the cortex there were many lymphocytes and scattered plasma cells. Peri vascular cuffing was prominent in the cortex, and in these vessels there was at times a tendency to invasion of the vessel wall by the lymphocytes which filled the perivascular spaces. In some of the cortical vessels there was a slight tendency to invade the vessel wall by the inflammatory elements. Hyaline changes were present in some arterioles. There was no pronounced arteritis. There was little glial reaction in the cortex, but gitter cells were found strewn among the other cells. There seemed to be some increase in the astrocytes, but the increase was not great. The process was a chronic meningo-encephalitis of a nonspecific nature, with a diffuse meningeal infiltration in which the characteristics of an acute tuberculous meningitis were lacking. There were no tubercles, no giant cells, and no vascular changes so frequently encountered in the acute phases of this disease.

DISCUSSION

Cases of tuberculous meningitis which terminate in recovery or in the development of a chronic course of the disease are characterized by one of two types of brain lesions.

In the one type, the meninges are thickened and show apparently, even after several years, a more or less typical tuberculous process. There may be granulomatous plaques in the meninges with caseation and a cellular and fibrous exudate in which macrophage elements predominate (Weidman (3)). Or there may be yellow nodules (Barth (4)) in which caseation still persists. Tubercles are present not infrequently in such cases even after several years (Janssen (5), Harbitz (6), Busse (7), Estramann (8), Rössle (9)). In some cases these tubercles have undergone some degree of organization with the subsequent development of fibrous nodules (Barth (4), and Brooks and Gibson (10)) or of fibrous tubercle-like nodules in which no exudate is visible (Brooks and Gibson). Sometimes the tubercles may become calcified (Leube (11), Estramann (8)) and produce so called calcified nodules in the meninges. In most of these cases there is little exudate in the fibrosis of the pia-arachnoid. Rarely however, as in the case recorded by Harbitz, there is rather extensive meningeal infiltration with lymphocytes and giant cells, as well as some perivascular and vascular infiltration. As a rule the vascular changes which are so characteristic of the acute cases of tuberculous meningitis are not found in these more chronic types.

In a second group of cases of tuberculous meningitis there is a different histological picture. Here the process is a diffuse chronic inflammatory lesion which bears little or no resemblance to acute tuberculous menin-

gitis. This is well exemplified by the case recorded here in which there was fibrosis of the pia-arachnoid, infiltration with lymphocytes and macrophages, and a diffuse encephalitis. In this particular instance there were no giant cells and no arteritis, though cases of chronic tuberculous meningitis with arteritis have been recorded (Ranke (12)). Foerster (13), who believes that a chronic meningeal infiltration due to tuberculosis is not rare, states that the histological picture in these cases reveals no typical tuberculous meningitis but a simple chronic fibrous formation with intensive cellular infiltration. The cases recorded by Ranke agree in general with these characteristics, except that vessel changes were prominent.

The two types of meningeal exudate which have been described in the chronic forms of tuberculous meningitis may have different antecedents. It is quite possible that the first group represents a chronic stage of the acute tuberculous forms which have not terminated fatally. In these, one sees merely acute tuberculous meningitis with chronic changes such as fibrosis of the meninges, and organization or even calcification of the tubercles. In the second group, however, there probably has never been a typical acute tuberculous meningitis. In these cases there probably has been from the start a nonspecific type of meningitis in a tuberculous individual. Due possibly to an invasion of the meninges by an attenuated form of the tubercle bacillus, or to some immune factor in the individual, the meningeal response in these cases has been different from the onset of the disease. Hence the absence of tubercles, giant cells, and of the typical vascular changes. If this is true, it is quite possible that cases of such chronic tuberculous infections of the meninges by tuberculosis are more common than we suspect.

CONCLUSIONS

1. A case of chronic tuberculous meningitis is recorded.
2. The histological characteristics of this case and of the other recorded cases in the literature are reported.

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THE ISOLATION OF ACID-FAST BACTERIA FROM SOIL[1]

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Rapidly growing saprophytic acid-fast bacteria are widely distributed in nature. They have often been demonstrated in soils, and several soil strains have been obtained in pure culture. The isolation of these microörganisms from soil has been difficult since they are present in very small numbers and, ordinarily, are quickly overgrown by a large variety of other microörganisms. Although several methods of isolation have been devised, the technique introduced by Söhngen has been the most satisfactory. Following Rahn's (1) demonstration of the utilization of paraffin as a carbon source by several molds, Söhngen (2) discovered that certain bacteria, including the mycobacteria, were also able to grow in a simple salt solution with paraffin as the only carbon source. Using Söhngen's technique, Büttner (3) found acid-fast microörganisms in 13 of the 17 natural substances tested. After failure to detect acid-fast bacteria in soil by means of direct smears, Frey and Hagan (4) tested several enrichment methods and obtained the best results with Söhngen's medium. They experienced, however, a heavy overgrowth of molds and actinomyces, which hindered attempts to isolate the acid-fast bacteria by plating or streaking. This difficulty was overcome by incubation of their soil cultures in Söhngen's medium at 47.5°C., a temperature above the maximum tolerated by molds and actinomyces, but not above that suitable for growth of the acid-fast saprophytes in their collection. By means of this modification of Söhngen's technique, they found acid-fast bacteria in 100 consecutive samples of soil from various parts of the United States and isolated 25 pure cultures by the streak method.

The method used by Frey and Hagan proved excellent for the isolation of thermoduric mycobacteria. Later study, however, of a larger collection of acid-fast saprophytes showed that many were incapable of growth at 47.5°C. This finding called our attention to the probability that such microörganisms existed in soil and were being missed by this

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technique because of their inability to develop at the high temperature used for elimination of molds.

The work reported in this paper was directed toward a modification of the technique of Frey and Hagan, in order to avoid the objectionable feature mentioned.

EXPERIMENTAL STUDIES

The point of departure was based upon Bruner's (5) observation that a number of saprophytic acid-fast microörganisms were capable of growth on a simple solution of inorganic salts in which there was no trace either of carbon or of nitrogen. Apparently these organisms are capable of utilizing carbon dioxide and either nitrogen or ammonia from the air as sources of carbon and nitrogen, respectively. Since Waksman (6) states that the ordinary nonsymbiotic fungi of the soil are incapable of extracting nitrogen from the air, it was thought that they might be checked while the acid-fast bacilli were being enriched by utilizing a nitrogen-free medium. This proved to be the case.

A study of 24 cultures, representing each of the groups of Thomson (7), indicated that all would grow in a modified Ashby's (8) solution, a nitrogen-free medium. Glycerol was substituted for mannitol; secondary potassium phosphate, for the primary phosphate, to raise the pH of the solution to approximately 7.8 and, perhaps, thereby restrain the molds. The medium as used had the following composition.

K_2HPO_4	0.2 gm.
$MgSO_4$	0.2 gm.
NaCl	0.2 gm.
$CaSO_4$	0.1 gm.
$CaCO_3$	5.0 gm.
Glycerol	15.0 gm.
H_2O	1,000 cc.

The salts were chemically pure; the water, distilled and free from ammonia. When tested for nitrogen by the micro-Kjeldahl method, not more than a faint trace could be detected.

The cultures used included *M. graminis*, *M. smegmatis*, *M. stercusis*, *M. phlei*, *M. leprae* (Elly, Brinkerhoff, Clegg), *M. berolinense*, Grassberger's butter bacillus, and several unnamed organisms isolated from soil. At room temperature these strains produced delicate, dull, surface films which gradually covered the surface of the medium and even pushed their way a considerable distance up the sides of the flasks.

We were interested to know if these organisms were able to fix atmospheric nitrogen in appreciable amounts. Several month-old cultures were subjected to analysis for nitrogen by the macro-Kjeldahl method. Two control flasks of the sterile uninoculated medium, one plugged with cotton, as were the cultures, and another sealed with a rubber stopper, were incubated and tested with the cultures. The results of these tests were as follows:

Culture	*Milligrams of nitrogen per cc. of medium*
No. 1 (*M. graminis*)	0.18
No. 8a (*M. phlei*)	0.16
No. 42 (culture from bovine lymph node)	0.17
Control (cotton stoppered)	0.15
Control (rubber stoppered)	0.12

It will be seen that the nitrogen accumulation in the cultures was insignificant, if, indeed there was any. Since the accuracy of the Kjeldahl determination is not greater than 0.1 mgm. of nitrogen, the slight apparent increase is within the limit of experimental error.

To proceed to the isolations: approximately 0.2 gm. of soil were inoculated into 25 cc. portions of Ashby's medium contained in small flasks. After 7 to 10 days' incubation at 25°C., a thin film of growth always appeared on the surface of the medium, consisting of rods and cocci, among which were a very few acid-fast forms. Since the acid-fasts were too few to be isolated easily, secondary enrichment cultures were made in Söhngen's medium which has the following composition.

K_2HPO_4	0.5 gm.
NH_4Cl	0.5 gm.
$MgSO_4$	0.2 gm.
Na_2CO_3	trace
H_2O	1,000 cc.

Carbon is supplied in the form of paraffin. In our work 5 cc. quantities of the solution of salts were placed in large test tubes and sterilized by autoclaving. When the tubes had cooled, paraffin coated glass rods, which projected above the surface of the fluid, were inserted.

Several loopfuls of the film from the Ashby's medium were added to this medium. After 7 to 10 days' incubation at 37°C. a band of bacterial growth, often highly pigmented, appeared just above the surface of the fluid. Smears from this material showed that 50 to 90 per cent of the organisms were acid-fast rods. A still greater concentration of acid-fast microörganisms frequently was accomplished by adding a few drops of sterile glycerol to the culture the day prior to

the end of the incubation period. Pure cultures of the organisms were readily obtained by plating from this growth on Dorset's (9) synthetic medium solidified with agar.

Dorset's Synthetic Medium

K_2HPO_4	1.0 gm.
$MgSO_4$	1.0 gm.
Na citrate	0.5 gm.
Asparagin	5.0 gm.
Ferric ammonium citrate	trace
Glycerol	70 cc.
H_2O	1,000 cc.

The incubation temperatures, 25°C. for the cultures in Ashby's medium and 37°C. for those in Söhngen's medium, gave the most satisfactory results.

By this method, 60 pure cultures of acid-fast organisms were isolated from 45 consecutive soil samples taken from a variety of local soils both fertilized and unfertilized. Only in the case of one sample of the 45 examined did mold growth appear, whereas Söhngen's medium inoculated directly with the same soil samples showed mold growth in 94 per cent of the tubes.

Twenty-seven of the 60 cultures isolated proved incapable of growing at 47.5°C. and, therefore, could not have been isolated with the technique of Frey and Hagan. The approximate 1:1 ratio of thermoduric to nonthermoduric forms indicates that the two types are about equally present in soil.

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RELATIONSHIPS BETWEEN FREE-LIVING THERMAL CILIATES AND INGESTED ACID-FAST BACTERIA[1]

LUCIA J. DUNHAM

A previous paper by the author (1) discussed the significance of evidence presented by White (2) and by Sabin and Doan (3) in regard to the multiplication of tubercle bacilli within certain phagocytic cells. The cells responsible for phagocytosis and lysis of tubercle bacilli were mononuclear cells of similar character. An attempt was made to investigate this difference in behavior toward tubercle bacilli from the angle of the immediate chemical environment of a phagocytic cell. A unicellular free-living ciliate, *Colpidium campylum*, was chosen for the experiment. A culture containing Colpidia and tubercle bacilli was carried in a 3 per cent glycerol medium, for glycerol is one of the substances most favorable to the growth of tubercle bacilli *in vitro* (4) (5) (6). No evidence of multiplication of tubercle bacilli within the protozoa was detected. No conclusive evidence of intracellular destruction of tubercle bacilli was obtained although at times apparently formless masses of acid-fast material were seen. As this appearance was not found in later work it was perhaps due to incomplete decolorization of contents of the protozoan food vacuole stained with carbol-fuchsin.

Since we observed extrusion of morphologically intact tubercle bacilli from the protozoa, we thought that a study of the fate of the ingested and extruded bacilli might indirectly throw some light on the question of mechanisms of cellular defense. Were the tubercle bacilli killed or changed in any other way by passage through the protozoa? Or, on the contrary, did culture with acid-fast bacteria exert any injurious effect on the protozoa?

While the present work was in progress, Rhines (7) published a paper on the possible rôle played by protozoa in the destruction of tubercle bacilli in nature. The growth of a ciliate isolated from soil, *Colpoda Steinii*, was supported in pure cultures of various bacteria at or near an optimum growth temperature of 23°C. A suspension of Avian 531,

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alone among several strains of pathogenic acid-fast bacteria, supported the growth of *Colpoda Steinii*, while the nutrient broth alone or the filtrate of a glycerol-broth culture of Avian 531 did not do this. The mechanism of the relation of *Colpoda Steinii* to Avian 531 was not entirely determined, as no morphological changes attributable to digestion were noted. Protozoa (*Colpoda Steinii* and *Colpoda cuculus*) exerted no pronounced destructive action on Avian 531, as evidenced by plate counts from cultures containing both protozoa and tubercle bacilli, and from control cultures without protozoa.

During the course of our work two closely similar bacteria-free and thermal strains of ciliates were used. These resembled *Colpidium campylum* of the earlier work but endured much higher temperatures. Thermal strains are a factor of possible importance when human or avian tubercle bacilli are used in an experiment and moreover are easier to maintain in circumstances when temperatures of 27° to 37°C. are encountered. The strains are described below.

The question of the action of protozoa on tubercle bacilli passing through their vacuoles was not completely answered. Approaches to this problem were as follows: a study of media suitable for culture of the protozoa, an orientation experiment to observe relationships between protozoa and 6 strains of acid-fast bacteria in 4 media and after various lengths of culture, a study of factors in ingestion by protozoa, attempts to observe individual living protozoa under the microscope and to see the large clumps of acid-fast bacteria contained in them, and observations on the effects of passage through protozoa on rough and smooth strains of human tubercle bacillus H37.

The protozoa: Dr. R. W. Glaser kindly furnished the thermal strain used in the major part of the work. He isolated this strain from Sulphur Spring at Hot Springs, Virginia, and with Coria described it in 1935 (8). Repeated tests proved the culture bacteria-free as they did in my work with them. Another ciliate, *Octagon*, also isolated from Hot Springs, was discarded in favor of the Sulphur Spring (SS) strain on account of the greater vigor with which the latter grew in the variety of culture media tried. Glaser and Coria found that the SS ciliates averaged 61 micra in length and 40.8 micra in width. The genus was classified by Professor D. H. Wenrich as *Saprophilus Stokes*, possibly *S. oviformis Kahl*, a species according to Hetherington (9) identical with *Glaucoma pyriformis*. The optimum growth temperature lay between 27° and

37°C. Our stock cultures were carried in 1 per cent peptone and 0.5 per cent NaCl in distilled water. This medium which we called *Standard II* was sterilized in test-tubes for 15 minutes at 20 lbs. (9 kg.) pressure, as were all the other media used except the sterile transudate mentioned below.

Another ciliate, morphologically and physiologically resembling *Saprophilus oviformis Kahl* and possibly identical with it, was used in the later part of the work for duplicating certain studies on the ingestion of tubercle bacilli and for the experiment with rough and smooth types of tubercle bacilli. This strain was obtained from a hot spring of 30°C., Agua Caliente, about 15 miles east of Tucson, Arizona. This will be referred to as the AC strain. It was grown out in Standard-II medium enriched by a suspension of *Bacterium coli* (10), and was washed by a combination of the techniques of Glaser and Coria (11) and of Parpart as modified by Hetherington (12), the latter technique for a single stubborn contaminant. The Standard-II medium was used in the washing. After this was completed, tests for sterile cultures were made on blood-agar and in glucose-broth at room temperature and at 37°C. The cultures were observed for two weeks and no contaminants were found. The ciliate was 40 to 65 micra in length and 15 to 30 micra in width. The optimum temperature for its growth was 28° to 32°C., although healthy cultures were maintained at 37°C. for 5 days. The AC strain grew well in the same media that had supported the SS strain. Transverse fission was observed in both strains, but no encystment was seen. Through the kindness of W. H. Furgason of Stanford University, California, the Agua Caliente strain has been classified as *Colpidium glaucomaeforme Sp. nov.*, described in 1935 by v. Gelei (13). This classification is based on a careful examination of the complex mouth parts, a method of study which Doctor Furgason (14) believes will probably lead in the future to a more accurate classification of the group of holotrichous ciliates.

Media used for protozoa: Cultures of the ciliates (SS) were sturdy and grew well, not only in Standard-II medium, but also when 3 per cent glycerol by weight was added to this medium. On the contrary, a concentration of from 4 to 6 per cent glycerol appeared to inhibit growth. The addition of 0.25 to 6 per cent gelatin to Standard-II supported healthy cultures, although the motion of the cells was slowed because of the increased viscosity of the medium. Growth was sparse but constant

in the Standard peptone-dextrose medium used in the work with *Colpidum campylum* (1), in Long's medium (15) diluted 1:10 with 2.5 per cent glycerol added, and in Penn's physiological medium (16) for freshwater protozoa. Sterile chest transudate from a case of cardiac decompensation was found to be an especially rich medium, undiluted or diluted with an equal part of sterile distilled water. Before the work of Rhines appeared attempts were made to find a medium in which the ciliates would not grow in the absence of bacteria but would flourish with bacterial contamination. If such a medium were found it was intended to substitute acid-fast bacteria for the contaminating organisms. Hay infusion, a common natural source of various protozoa, was tried. One of the two tubes of autoclaved 0.5 per cent hay infusion was left open to the air for 24 hours, the other was left stoppered. They were then inoculated with SS protozoa and two days later both the sterile and contaminated tubes showed a 1+ growth of protozoa (3+ designates a maximum growth of healthy protozoa), but the next day the ciliates were dead in both tubes.

Orientation experiment: An orientation experiment was carried out to observe possible differences in behavior of protozoa acid-fast cultures in various media and after varying lengths of culture. Six strains of acid-fast bacteria were used, Avian 4, Leprae Clegg, Leprae Duval, H37, Marinum 1, and HPI Phlei (Timothy). These had been obtained from Dr. Esmond R. Long at the Henry Phipps Institute in Philadelphia. Test tubes containing 3 day cultures of SS protozoa in the following media, Standard II, Standard II with 2.5 per cent glycerol, Standard II with 5 per cent gelatin, and sterile chest transudate diluted 1:1 were inoculated with the suspensions, in approximately equal concentration,

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FIG. 1. Sample taken from a 14-day culture of the Sulphur Spring strain of protozoa with Avian 4. The medium is sterile transudate diluted with an equal quantity of sterile distilled water. Although these protozoa are negatively geotropic they also show positive chemotropism to the particulate matter in the test tube, a fact which explains the rather unusual concentration of cells in this sample taken from the bottom of the tube. All but a few protozoa are loaded with dark clumps of tubercle bacilli gathered chiefly at the blunt posterior end of the cell. A few of these are seen outside the cells. Rare single bacilli can be distinguished intracellularly. The preparation, stained by the Ziehl-Neelsen technique, shows red clumps against a background of blue protoplasm. (× 650)

FIG. 2. A single ciliate of the Agua Caliente strain from a 5-day culture with tubercle bacillus H37X in a 1 per cent peptone, 0.5 per cent sodium chloride medium. Individual tubercle bacilli can be made out in some of the intracellular clumps and faintly in the surrounding medium. Ziehl-Neelsen stain. (× 2,000)

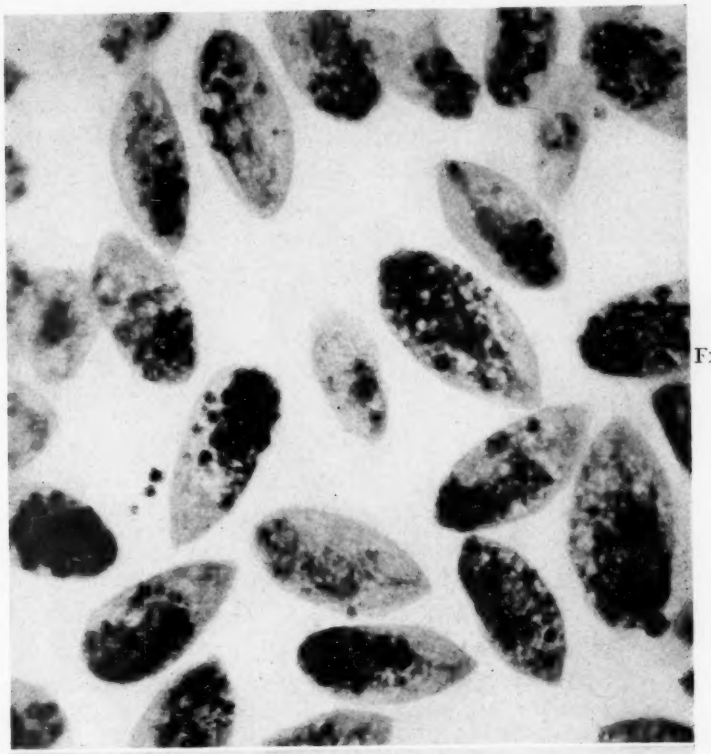

FIG. 1

FIG. 2

PHOTOMICROGRAPHS

of the 6 strains of acid-fast bacteria. Control cultures of protozoa and also of the bacilli were followed. The tubes were kept at room temperature to prolong the life of the protozoa and so of the experiment. The contents of the tubes were shaken at frequent intervals. After 1, 2, 5, 9, 14 and 22 days, and again at 5 and 7 weeks in the few cultures still showing living protozoa, samples were taken from the top third of the tubes where the negatively geotropic ciliates collect. The drops were placed on slides, dried in air, fixed with methyl alcohol and stained by the Ziehl-Neelsen technique, steaming with carbol-fuchsin for 2 minutes and counterstaining with a 1:80 dilution of a saturated alcoholic solution of methylene-blue. These samples were studied individually and in relation to the whole series. Protozoan growth was most luxurious in the Standard II with 2.5 per cent glycerol and the transudate media, and these cultures were followed with special interest.

The presence within the protozoa of large round clumps of acid-fast bacteria as well as of single bacilli was striking. In fixed and stained samples the clumps were mainly grouped at the blunt posterior end of the cell. Figures 1 and 2 represent typical examples of this picture. These clumps, although they call to mind the globi of leprosy which have a slightly larger average size (5 to 8 micra instead of 2 to 5 micra) are undoubtedly aggregations of the bacilli in the digestive vacuoles of the ciliates. Leprae Duval which is longer than the other acid-fast bacteria was grouped in bundles rather than in globular clumps. No morphological changes in any of the intracellular bacilli were observed.

Examination of stained preparations gave no evidence that the different media used significantly altered the picture of ingestion. In samples from the transudate medium, extrusion of clumps of bacilli appeared earlier than in the other media, either because of the physical nature of this medium or because it speeded up the metabolism of the protozoa. There were no conspicuous variations in the behavior of the protozoa toward the 6 strains of acid-fast bacteria. Samples of the cultures taken at different times after the inoculations did not differ strikingly from one another. However, we were left with the impression that the number of intracellular bacilli and the size of the clumps decreased after the first few days of culture. Later some samples showed larger clumps outside the cells than inside. Samples of the few cultures still living at 5 and 7 weeks showed only occasional intracellular bacilli and small clumps. The control cultures of protozoa alone lived no longer, which would indicate a benign relationship of acid-fast bacteria to

protozoa. No significant clumping, multiplication or destruction was observed in the controls of acid-fast strains in the four media.

Factors in ingestion by protozoa: A few factors in the ingestion of acid-fast bacteria were studied. This ingestion was compared morphologically with that of *Bacterium coli* and *Staphylococcus albus*. Cultures with all three microörganisms flourished equally well. Samples taken at 24 and 48 hours were stained and examined. No distinct morphological picture of ingestion was seen with the latter two bacteria. Butterfield (17) has shown that "Colpidium can depend upon bacterial cells as a sole source of food and that they utilize them when they are available." Ingestion and digestion of these non-acid-fast bacteria were probably relatively very rapid. In another experiment acid-fast bacteria were killed by heat and also chemically (1.5 per cent phenol). When ingested by protozoa, these killed bacilli did not differ in morphological appearance from ingested living bacilli. Differences in dosage, as between one part and four parts of suspensions of acid-fast bacteria, did not change the picture of ingestion.

In pictures such as that in figure 1 in which living protozoa are in contact with apparently extruded clumps of bacilli, the question arose of possible reingestion of some of these extruded clumps. If this occurred the mechanism of digestion by ciliates, whether effective or not, would be exerted on the acid-fast bacteria over a longer time period. The capacity of the protozoa to ingest large particulate matter was investigated. Whole human red blood cells, although they average 1 to 2 micra larger than the acid-fast clumps, were chosen for the experiment. One cc. of a suspension of fresh red corpuscles in physiological (0.85 per cent) saline was inoculated with one drop of a flourishing protozoan culture in 1 per cent peptone, 0.85 per cent sodium chloride in distilled water, and left at room temperature. After 5 hours the tube was shaken and a sample drop taken. This was repeated at 24 hours. These drops were dried in air and stained lightly by Wright's technique. In both samples many vacuoles in the majority of cells were distended with red material resembling discrete erythrocytes in size and shape. In the 24-hour sample some vacuoles had decreased in size and contained a green staining substance, apparently a digestion product of the original haemoglobin. Upon sedimentation of the cells in the tube, the supernatant fluid remained clear and colorless. No gross haemolysis had taken place. In a control tube, one drop of protozoa was added to a definitely red

solution of haemolyzed red cells, which had been adjusted after haemolysis to a saline concentration of 0.85 per cent. Food vacuoles stained in samples taken at 2 and at 24 hours were small and slightly pigmented with haemoglobin, never round and swollen. The work indicated that the protozoa can under some circumstances ingest large particulate matter, and may be able to reingest extruded clumps of tubercle bacilli.

Attempts to observe individual living protozoa and contained clumps of acid-fast bacteria: Observation of individual living protozoa over periods of several hours or better of several days, and means of distinguishing between those which contained clumps of acid-fast bacteria and those which did not, seemed of prime importance in studying the fate of the bacteria. The protozoa were difficult to study because of the darting rapidity of their motion and the constant multiplication of cells in healthy cultures. The often described "foam" or "soap-bubble" structure of protoplasm made the contents of individual vacuoles very hard to distinguish in the living ciliate.

Attempts to slow the motion of individual cells were varyingly successful. Relatively crude methods such as the pressure exerted by a coverslip were discarded in favor of increasing the viscosity of the medium. In 12.5 per cent nutrient gelatin the speed was slowed to about one-fifth of normal but the cells were distorted. Eight per cent gum arabic slowed the speed to approximately one-tenth of normal. More satisfactory then either of these was a solid agar-gelatin-glycerol medium. A medium containing 1 per cent agar, 5 per cent gelatin, and 3 per cent glycerol made up in Standard II gave the maximum limitation of growth of protozoa with the minimum distortion of individual cells. Plates of this medium were inoculated with ciliates by means of a sterile platinum loop. Drying of the medium was postponed by the inversion of the plates and the addition of sterile water to the covers. Cultures were examined at intervals through a dissecting microscope. The protozoa were seen in small groups at or near the surface of the medium. Motion and multiplication were definitely limited for 2 or 3 days after which time individual cells died while others multiplied rapidly in pockets of the liquefied medium, living in crowded swarms for about 5 days more. In another experiment protozoa were examined under high power on the same medium, a fluid drop of which was placed in a depression slide. After solidification the medium was inoculated with three or four protozoa and the culture covered with a sterile coverslip and

sealed with paraffin and vaselin. The coverslip did not quite touch the surface of the medium. The cells could be watched in this way for about 24 hours after which time they died as a result of drying. Sealing one or two protozoa in a small drop of nutrient fluid medium offered no advantages, for although the cells lived longer, they moved and multiplied more rapidly.

Chejfec (18) prolonged the life cycle of *Paramecium caudatum* so that this ciliate lived but division did not occur, by gradually diminishing the bacterial suspension of the infusion. This suggested to us variation of the peptone concentration of the Standard-II medium. Five concentrations were made up, from 0.2 per cent up to the usual 1 per cent. The inoculum was sufficiently heavy so that a 1+ growth was visible in the tubes at the time of inoculation. It increased to 2+ growth in all tubes and fell off rapidly to no growth in the two lowest concentrations. This was obviously not a satisfactory method of maintaining these ciliates while limiting multiplication.

Attempts to see the contents of food vacuoles in living protozoa, particularly when the vacuoles contained large clumps of tubercle bacilli, were first made in light and dark microscopical fields. Protozoa were also examined by the diffuse lighting in the depression slide culture with agar-gelatin-glycerol medium. A striking feature of the stained preparation was the dark rigid appearance of the vacuoles filled with acid-fast bacteria. It is surprising that no constant differences could be seen between living preparations from cultures of protozoa with and without suspensions of tubercle bacilli.

Vital staining was then tried. Safranine, methyl-green, methyl-blue and janus-green were all unsatisfactory because of definite toxicity and a diffuse type of staining. Although brilliant cresyl-blue and methyl-violet were not very toxic, the staining was again found to be diffuse. Neutral red was more satisfactory. It was used in dilutions of 1:550,000 in fluid culture, and of 1:200,000 in the agar-gelatin-glycerol medium. Protozoa inoculated to these media assumed definite flecks of the red stain. Theoretically the contents of a food vacuole if digested should stain with neutral red. We wished to find out if the swollen food vacuoles containing tubercle bacilli also contained neutral-red. A few protozoa were picked from a stained fluid culture of SS with avian tubercle bacilli and placed in a drop on a slide. Before death of the protozoa from drying, stained areas represented by the definite flecks of red mentioned above were watched and counted. No adequate correlation

was observed between the number and distribution of the flecks of dye and the vacuoles later proved to be filled with acid-fast bacteria. In further studies three food colors, red, blue and green, sold commercially in liquid form were used. These were not toxic to the ciliates in dilutions of from 1:200 to 1:400 but stained the protoplasm diffusely. Semenoff and Maslowa (19), although successful in staining the vacuoles of *Paramecium caudatum* intravitally by feeding *Bacillus prodigiosus*, report a lack of clear color gradation when this technique is used with small ciliates.

Experiment with rough and smooth strains of human tubercle bacillus H37: In view of the fact that we still had no clear picture of the fate of ingested and extruded acid-fast organisms, we thought we might study the problem from the point of view of changes that might be induced in acid-fast bacteria subjected to passage through protozoa. Rhines had found evidence that certain acid-fast bacteria furnished something essential to *Colpoda Steinii*, but no evidence of significant destruction of these bacilli. Several studies have recently been made on rough, smooth and intermediate types of colonies among tubercle bacilli. These three morphological types are described by Smithburn (20). Chief factors in colony variation appear to be the type of media (21), the pH to which the bacilli are subjected (22), factors of light, temperature, CO_2 and O_2 tension (23), and at times the results of passage in laboratory animals (20).

We wanted to know if typical rough and smooth colony types in the morphological sense, for example H37 and H37X, would show changes in colony type after passage through protozoa. A culture of H37X was obtained from Dr. Max Pinner (24) who described this glistening smooth colony strain which grew out from H37 when a culture of the latter was heated to an unknown degree for an undetermined length of time but for less than 16 hours. H37X is a rapidly growing acid-fast bacillus producing benign and self-healing lesions in laboratory animals. Twice after serial animal transfer in guinea pigs, Pinner produced typical inoculation tuberculosis and recovered typical rough growing human tubercle bacilli. In our experience there were no striking differences noted in the microscopical morphology of H37 and H37X. They were relatively stable rough and smooth strains presumably of the same organism. H37X had been carried an unknown number of generations on Petragnani's medium as quoted by Pinner (25), and H37 for two

generations. All the colonies of H37X on this medium were smooth. About 75 per cent of the colonies of H37 were rough and coarsely granular, the remainder intermediate or stippled, flat and spreading.

Six weeks' cultures of the tubercle bacilli and 3-day cultures of AC protozoa in Standard II of an initial pH of 6.0 were used. Tubercle bacilli removed from the slant were shaken with glass beads in 2 cc. of Standard II of pH 6.0. Necessary dilutions of the two suspensions were made until thin smears carefully handled and stained by the Ziehl-Neelsen technique showed approximately the same average concentration of bacilli per oil immersion field. H37X was uniformly suspended, while H37 showed in addition to single bacilli many small irregular clumps. Smithburn (22) has suggested the wisdom of not eliminating possible variants with a tendency to clump, and these clumps were not filtered out. Controlling the original suspensions, 0.15 cc. of each was inoculated directly to tubes of Petragnani's medium, spread over the surface of the slant and allowed to dry for 12 hours before the final paraffin seal was applied. By the application of the quinhydrone method described by Steenken (26) the pH of all the Petragnani's medium used in the experiment was determined to be 6.3.

One cc. of each of the suspensions of tubercle bacilli was inoculated into each of two tubes containing cultures of protozoa in 5 cc. of Standard II, and into each of two tubes containing 5 cc. of Standard II alone. Half of the tubes, duplicating the remainder (AC + H37, AC + H37X, H37 alone, and H37X alone) were subjected to regular mixing at intervals of about 8 hours over a period of 4 days. At the end of this time protozoan growth appeared to be diminishing. The pH of each tube was then adjusted to 6.3. In this way the inoculations to Petragnani's medium were always made from a medium of the same pH (22). Inoculations of 0.15 cc. were made to tubes of Petragnani's medium from the undiluted culture and from dilutions of 1:6 and 1:12.

The remaining four tubes were left undisturbed for 48 hours. One cc. of the culture or suspension was removed from the surface of each tube and added to corresponding tubes containing 5 cc. of fresh Standard II. The contents of these fresh tubes were then mixed at regular intervals for four more days, the pH was adjusted to 6.3 and inoculations to Petragnani's medium were made corresponding to the 1:6 and 1:12 dilutions above. Transfers were made from the surface of previous cultures in the belief that by sedimentation all or most of the bacilli that had not come in contact with the protozoa through ingestion or recent

extrusion by them would be eliminated. A sample drop stained at the time of transfer showed that the bacilli were mainly within the cells in the cultures with protozoa.

The Petragnani cultures were observed at 4, 6, 8, 11 and 16 weeks. Colony counts were made where possible, and where not possible estimates of acid-fast growth were made. The growth of H37X appeared earlier and was more luxurious throughout than that of H37. Cultures from the protozoa with contained bacilli transferred to a fresh medium showed no differences from the other cultures. Significant findings were: (*1*) No diminution in colony counts in the seeding from protozoa acid-fast cultures in contrast with the corresponding suspensions of acid-fast bacteria alone. It will be remembered that Rhines found no conspicuous destructive action of protozoa on tubercle bacilli. (*2*) No convincing changes in colony types or proportions of colony types were noted. The growth of H37X was smooth, the proportion of rough and intermediate colonies in H37 cultures was approximately as before. Rough and smooth acid-fast strains growing on solid media after intimate contact for four days with protozoa in fluid media showed no changes in colony type.

DISCUSSION

A study of relationships between free-living thermal ciliates in bacteria-free culture and acid-fast bacteria ingested by them was made in the hope that it might throw light on the question of the mechanisms of cellular defense. Digestion of tubercle bacilli by protozoa was a problem raised as far back as 1912 when Métalnikoff (27) fed *Paramecium* a suspension of tubercle bacilli colored with congo-red. The contents of the vacuole changed from alkaline to acid and back to alkaline. Métalnikoff suggested that certain easily assimilable substances might be obtained from the bacilli, although he did not believe that tubercle bacilli supplied with a "lipoid membrane" could be digested. Rhines was able to support growth of *Colpoda Steinii* in a nutrient broth culture of Avian 531. On the other hand he found no morphological evidence of digestion.

Acid-fast bacteria are carried by protozoa in food vacuoles in which many non-acid-fast organisms are digested. The influences that the bacilli may be subjected to in the vacuoles may be mentioned. In 1925 Shapiro (28) using phenol-red, congo-red, neutral-red, and litmus as indicators followed the pH of the gastric vacuoles of *Paramecium* from

7.6 to 4.0 and back to 7.0. Howland (29), studying *Actinosphaerium Eichhornii* which depends on living food, finds a lowered pH during digestion and in vacuoles containing indigestible remains. It is interesting that Rous (30) estimates from studies *in vivo* with brom-phenol-blue that certain parts of the macrophage have a pH as low as 3.0.

We felt it was important to study the exact fate of ingested tubercle bacilli. Rhines's colony count studies of suspensions of acid-fast bacteria in the presence and absence of protozoa and similar work in our experience indicated that the protozoa do not exert a definitely injurious effect on the bacilli. Rough and smooth forms of human tubercle bacillus H37 were not altered by passage through protozoa. As the rough and smooth forms chosen were relatively stable, this does not absolutely preclude possible alterations in colony types growing from acid-fast bacteria which have been in the food vacuoles of protozoa.

SUMMARY AND CONCLUSIONS

1. In an orientation experiment large round clumps of tubercle bacilli were seen intracellularly in fixed and stained specimens from protozoa acid-fast cultures in fluid media. These clumps were apparently at times extruded from the ciliates. Neither the 4 fluid media used nor any of the 6 strains of acid-fast bacteria varied this picture of ingestion significantly. No morphological changes were noted in ingested acid-fast bacteria in cultures observed for as long as 7 weeks, although the intracellular clumps decreased in size during this period.

2. In the same experiment the length of life of cultures of thermal ciliates was approximately the same with and without the addition of various strains of acid-fast bacteria, indicating a benign relationship of the bacteria to the protozoa. Conversely, a fact which appeared in an experiment with rough and smooth strains of bacilli, colony counts from seedings of protozoan cultures with and without tubercle bacilli indicated that the protozoa exerted no conspicuous destructive action on the tubercle bacilli.

3. Rough and smooth forms of human tubercle bacillus H37 were not altered by passage through ciliates.

4. Media suitable for ciliates are discussed. Ingestion of micro-organsims other than acid-fast bacteria, of killed tubercle bacilli, of suspensions of tubercle bacilli of varied concentration, and of large particulate matter are described. Attempts to observe individual living protozoa by slowing their motion and by diminishing the nutrient con-

tent of the medium to discourage multiplication were made. Attempts to observe intracellular clumps of tubercle bacilli in the living cell were tried with various types of illumination and with vital staining.

5. The exact fate of ingested bacilli was not decided.

6. Thermal ciliates in bacteria-free culture offer for study a medium which is both flexible and subject to definite limitations.

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RED-CELL SEDIMENTATION IN PULMONARY TUBERCULOSIS[1]

RALPH VOLK

The purpose of our investigation of the erythrocyte sedimentation rate was to determine its correlation with temperature, pulse, the occurrence of haemoptysis, the bacillary content of the sputum and with clinical activity. This, we hoped, would establish the reliability of that test as an aid in determining the activity of disease in a tuberculous patient. If of sufficient value as an adjunct to clinical criteria, it was to be adopted as a routine procedure; if not, it was to be discarded.

Once a diagnosis of pulmonary tuberculosis is made, the next important decision is whether the disease is active, and to what degree.

The patient presents subjective and objective symptoms and signs, and we have at our disposal the X-ray and sputum examinations, which, if positive, tell us that a given patient has active tuberculosis. We know, however, that there is often an active or smouldering disease in a patient with normal temperature, a pulse that is not too elevated, a negative sputum, and a series of X-ray films which show no definite changes to indicate that a process has quieted down.

The basis of treatment lies in the activity of the disease, whether the form of treatment be general rest, pneumothorax, phrenicectomy or thoracoplasty.

The time to discharge a patient from the sanatorium depends primarily on the ability of the phthisiologist to say that his disease is quiescent or arrested. This period of discharge is more important to the patient than is the method of treatment by which he has reached that goal. He wants fair assurance that his disease will not become reactivated and require his readmission to a hospital just as he is becoming readjusted to a normal life.

We, therefore, welcome any procedure which will help in determining that a given case is inactive. We decided to study the sedimentation eaction in preference to white cell counts and monocyte-lymphocyter ratios because it is less time consuming, and there is probably more

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chance for uniform results, particularly when several men do the test in the same institution.

METHOD

Of the several methods of determining sedimentation of red blood cells, we chose the Cutler method in preference to others because Cutler has classified his reactions into groups indicating varying degrees of activity of disease. This method, devised by J. W. Cutler of Philadelphia, combines the distance and time methods, taking readings of the level of the red-cell column at five minute intervals for a period of one hour. Citrated blood is used, 0.1 cc. of 3 per cent solution of sodium citrate for each 0.9 cc. of blood.

The citrate, which has been filtered and autoclaved, is drawn into the syringe first and then the blood withdrawn from a vein. Although only 1 cc. of blood is required for the test, we withdraw 2 cc. to allow for loss in transfer to the sedimentation tube. The Cutler tube is of 1 cubic centimetre capacity and graduated in millimetres down to 40. Before transferring the blood from the syringe to the tube, the syringe is inverted several times to mix the blood and citrate.

Two terms, as used by Cutler, should be defined before we describe the types of curves which may be obtained:

1: Sedimentation time is the time required for "complete" settling of red cells.

2: Sedimentation index is the total sedimentation of red cells at the end of an hour, expressed in millimetres.

The figures obtained at the several readings are plotted on a graph and will then be represented by one of four types of "curves."

The first, or *horizontal line,* is the normal curve showing an "index" of 10 millimetres or less.

The second, or *diagonal line,* has a sedimentation index of 10 to 20 millimetres, but sedimentation is not complete in 60 minutes; or, in other words, "sedimentation time" is longer than one hour.

The third, or *diagonal curve,* has a reading of 20 millimetres or more at the end of an hour, and a sedimentation time between 35 and 55 minutes.

The fourth, or *vertical curve,* has an index of 20 or more and a sedimentation time of 35 minutes or less.

According to Cutler, the various curves indicate varying degrees of

activity of disease. The horizontal line is the normal curve indicating inactivity or quiescence. The diagonal line indicates slight activity; the diagonal curve, slight to moderate activity; the vertical curve, marked activity.

There has been no formula devised for transposition of values obtained by one method into terms of another. It is, therefore, compulsory that we repeat tests on a given patient always by the same procedure.

RESULTS

After doing over 1,000 sedimentation determinations, we decided that we should be able to draw some conclusions as to its agreement with our clinical findings and its value in determining the degree of activity of tuberculous disease. We have gathered statistics on these cases with

TABLE 1

Comparison of sedimentation rate and temperature

	NORMAL	98.6°–99°	99°–100°	100° OR OVER
Horizontal line	27.1%	12.8%	0.7%	0
Diagonal line	34.8%	20.9%	8.0%	3.6%
Diagonal curve and vertical curve	37.9%	66.1%	90.5%	96.3%
Total number of cases	682	148	137	55

reference to temperature, pulse, haemoptysis and presence or absence of tubercle bacilli in the sputum. We have also listed the cases which died subsequently and have compiled another group which we termed "clinically active." For practical purposes we have combined the diagonal curves and vertical curves representing the more active sedimentations.

In table 1 we see that there are more than twice as many horizontal lines or normal sedimentations in patients with temperatures up to 99°F. and only 0.7 per cent of patients with temperatures of 100°F. or more with this type of curve. In the diagonal line, or slightly active group, we find that as the temperature goes up there is a fast drop in percentage of diagonal lines. When we come to the diagonal curve and vertical curve, the moderately and markedly active curves, there is a fast rise in these types of curves as the temperature rises.

Table 2 shows that, as the pulse rate rises, the percentage of horizontal lines or normal curves decreases. The percentage of diagonal

lines, or slightly active curves, is higher with pulse rates of 80 to 90 than with pulse rates of 80 or less, but is smaller in patients with pulse rates above 90.

The percentage of diagonal and vertical curves rises very definitely as pulse rates increase.

In table 3 we have included all cases of frank haemoptysis or of streaking within three months of the time that the sedimentation rate was determined. We find that the vast majority of all these patients, a total of 91.4 per cent, had sedimentation rates indicating some degree of activity.

TABLE 2

Comparison of sedimentation rate and pulse rate

	80 OR UNDER	80–90	90–100	100 OR OVER
Horizontal line	44.2%	25.1%	15.1%	5.6%
Diagonal line	30.7%	34.4%	23.6%	12.7%
Diagonal curve and vertical curve	25.0%	40.4%	61.0%	81.5%
Total number of cases	52	478	350	141

TABLE 3

Sedimentation rates in patients with haemoptyses

HORIZONTAL LINE	DIAGONAL LINE	DIAGONAL CURVE AND VERTICAL CURVE
8.4%	29%	62.4%
Total number of cases		165

In the positive sputum group, 5.6 per cent had horizontal lines, 24.7 per cent had diagonal lines, and 69.4 per cent diagonal curves and vertical curves. Combining all increased sedimentation rates, a total of 94.1 per cent showed some degree of activity of disease.

We felt that 5.6 per cent of positive-sputum cases with a normal sedimentation was rather high and required further investigation. Twenty-four patients comprised this group. In going over their charts, we found that 8 turned negative shortly after the sedimentations were done and remained negative since, a period of at least eight months in each case, and over a year in most of them. Nine cases were considered well enough clinically to be fully ambulant and were in "camps," and 3 of these were working on the wards. Three cases showed increased sedimentations subsequently.

This accounts for 20 of these 24 patients. Of the remaining 4, 1 showed remarkable clearing of his tuberculous process by X-ray, from an involvement of two-thirds of the right lung and one-third of the left with bilateral cavitation to small fibroid and calcified areas in both infraclavicular regions. The second case had a bilateral upper thoracoplasty with cavities remaining open. The third case died two years later with symptoms of meningitis. The fourth case died over a year later of cardiorespiratory failure following a massive pleural effusion.

TABLE 4

Comparison of sedimentation rate and bacillary content of sputum

	POSITIVE	NEGATIVE
Horizontal line	5.6%	43.8%
Diagonal line	24.7%	32.6%
Diagonal curve and vertical curve	69.4%	23.4%
Total number of cases	633	383

TABLE 5

Sedimentation rates in fatal cases

HORIZONTAL LINE	DIAGONAL LINE	DIAGONAL CURVE AND VERTICAL CURVE
1.4%	9.2%	89.2%
Total number of cases		140

TABLE 6

Sedimentation rates in clinically active patients

HORIZONTAL LINE	DIAGONAL LINE	DIAGONAL CURVE AND VERTICAL CURVE
3.4%	22.7%	73.7%
Total number of cases		553

There were 140 deaths among the patients on whom we had determined sedimentation rates. Of these, 1.4 per cent showed horizontal lines, 9.2 per cent slightly active, and 89.2 per cent of the more active curves; 98.4 per cent showed some degree of activity of disease as indicated by the sedimentation rates. These figures would indicate that repeatedly active sedimentations on a patient may be of some prognostic value.

In table 6 we have included all patients having a combination of any two of the following positive findings: (*1*) temperature of 99° or more; (*2*) pulse of 90 or more; (*3*) haemoptysis or streaking within 3 months of the test; (*4*) positive sputum. We considered this to be fair evidence of the presence of active disease. A total of 96.4 per cent had sedimentation rates indicative of some degree of activity.

CONCLUSIONS

Study of the results obtained on 1,000 sedimentation determinations shows a definite parallelism between clinical findings and sedimentation rates. Patients having clinical signs of active disease present the greatest percentage of "active curves." There was agreement to the extent of 85 to 99 per cent, which, I believe, is as close a check as any one can hope for in a nonspecific procedure.

There seems to be definite evidence that red-cell sedimentation can be a valuable adjunct to other routine procedures in the clinical study of tuberculosis. We have found it of considerable value in pneumothorax and thoracoplasty cases, where X-ray films may give us no more information than that a certain amount of collapse of the lung exists.

A repeatedly elevated sedimentation rate, with no clinical signs of activity of tuberculous disease, requires a more careful study of the X-ray films, more thorough examinations of sputa, and, if these continue to be negative, the patient should be investigated for other causes of an increased sedimentation rate.

The red-cell sedimentation should not be depended upon exclusively because there are other factors to alter the test in individual cases, such as severe anaemia, pregnancy and intercurrent infections; but the test has shown itself of sufficient value to be included as a routine procedure in tuberculosis sanatoria.

EDITORIAL

Is the Decline in Tuberculosis Arrested?

Has the decline in the death rate from tuberculosis been checked? Recent mortality reports raise this question. The steady decline in the mortality from tuberculosis which has taken place during recent decades has led many of us to believe that the disease would shortly be relegated to a minor position among the causes of death. Have we perhaps been overoptimistic?

When the mortality reports covering 1935 for the entire country became available recently, it was found that the tuberculosis death rate was only 2.8 per cent lower than it had been in 1934, whereas during the previous year the drop equalled 4.9 per cent. At the same time, a similar slowing up of the decline in tuberculosis has been observed among the 17,500,000 Industrial policyholders of the Metropolitan Life Insurance Company, a group which constitutes a fair cross-section of the urban population of the country. Among these policyholders, it became evident, in the latter half of 1936, that the downward swing of the tuberculosis rate was being checked. For, during that year, the rate declined only 2.9 per cent, whereas it had dropped 6.1 per cent between 1934 and 1935 and 8.2 per cent between 1933 and 1934.

Through the courtesy of State health officials, the Metropolitan Life Insurance Company has received provisional mortality figures for tuberculosis for the year 1936 from 40 States. Of these there were just 19 which reported a mortality for 1936 higher than that for 1935, and 19 which reported lower figures; two showed no change. Whichever way the balance will be found to tilt when final results for all the States are in, this much is sure, that the margin of increase or decrease over the preceding year will be small. Even if we do not have to record an actual rise, there certainly has been a definite check in the velocity of the decline in tuberculosis mortality which has been going on continuously over a number of years past, particularly during the last decade.

The depression years were, in a very real sense, the most remarkable ones in the history of the campaign against tuberculosis in the United States. As was inevitable, the people, as a whole, were faced during this period with more worries and perplexities than ever before. There

were the problems of insufficient or improper food; millions of people lived in congested quarters and endured other hardships. Environmental conditions in general were such as would be expected to cause an increase rather than a decline in deaths from tuberculosis. Instead, the mortality rate not only continued to fall during these years of economic maladjustment but it actually fell at a faster rate than during the predepression years. Now, with economic conditions definitely improved, it appears that the decline has either ceased altogether, or, at best, that it has become negligible.

The question which arises is whether the present situation of the tuberculosis death rate is an aftermath of the depression. Has there been an impairment in American vitality, which did not become manifest until the depression itself had lifted? Public health workers have feared that this very contingency might arise. It is certain that the current situation has not been due to any abatement in the efforts toward tuberculosis control; for there has been no let-down. On the other hand, as the death rate approached lower figures a gradual slowing up of the rate of decline was to be expected, since it may be assumed that there is an irreducible minimum for tuberculosis deaths. The stoppage has been too abrupt to be accounted for in this way. Furthermore, there is no reason to believe that the present death rate from tuberculosis, in the United States, as yet approaches this irreducible minimum, as is indicated by the fact that the general tuberculosis death rate is more than twice that reported in a number of States.

Perhaps an explanation of the sudden reduction in the rate of decline lies in the fact that during the depression large numbers of persons with quiescent or incipient tuberculosis were subjected to enforced idleness through the lack of available jobs. This kept such persons in comparatively good health and helped to reduce tuberculosis mortality during the depression. As industrial conditions improved, however, many of these potentially tuberculous persons availed themselves of the increased opportunities and accepted jobs more or less suited to their state of health. Naturally, a certain number, overestimating their strength, succumbed to the strain and stress of modern business life; the consequences of which are now being reflected in the rising death rate. Unfortunately, as yet there are no data available which enable us to test the truth of this theory. For the present, we shall have to be satisfied with its reasonableness.

One thing is certain, we shall have to make radical changes in our present methods of dealing with tuberculosis before we can hope for further substantial gains against the disease. In the first place, we must give more attention to the social and economic rehabilitation of patients discharged from sanatoria as arrested cases. Such persons are physically, mentally and psychically unfitted to compete with healthy persons under modern industrial conditions. Many employers are unwilling or afraid to hire such persons. As a result, they usually drift about seeking any employment that they can find, eventually landing in a job badly adapted to their physical condition. Sooner or later there follows a relapse and a return to the sanatorium with far advanced disease.

Common sense would seem to dictate a change in this wasteful course. Of what use is it to spend thousands of dollars arresting a case of tuberculosis only to return the patient to the same environment and working conditions originally responsible for his illness? Future advancement in the control of tuberculosis demands that the care and protection of discharged patients shall not cease until their social readjustment is firmly established.

Other procedures which must be stepped up before we can hope for real eradication of the disease are intensified methods for locating open cases of infection, greater concentration of effort among Negroes, and improved regulation of the unhygienic conditions in certain industries.

In a word, continued progress in the eradication of tuberculosis calls for an intensified campaign conducted with far more intelligent concentration than has been applied to the problem in the past. The nearer we approach the goal, the more strenuously will we have to strive for its attainment.

L. I. D.

THE EVOLUTION OF DISPENSARY CONTROL OF TUBERCULOSIS[1]

Historical Aspects

JABEZ H. ELLIOTT[2]

The happy possessor of a copy of "The Dispensary: A Poem," in Six Cantos, London, 1699, may read in Samuel Garth's preface a reference to "Erecting the Dispensary, being an Apartment in the College set up for the Relief of the Sick Poor, and managed ever since with an Integrity and Disinterest suitable to so Charitable a Design. If any Person wou'd be more fully informed about the Particulars of so Pious a Work, I refer him to a Treatise set forth by the Authority of the President and Censors in the Year 97 't is called A Short Account of the Proceedings of the College of Physicians, London in relation to the Sick Poor." Then follows the Instrument dated December 22, 1696, subscribed to by the President and Fellows to the number of fifty-three, obliging themselves to pay the sum of ten pounds apiece for the carrying on of the Dispensary.

Among the fifty-three subscribers to this Dispensary opened in the College of Physicians, and the first dispensary in the English speaking world, appear the names of some who might well be recalled. There were Thomas Millington, the President of the College; Thomas Burwell who received and expended the money; Edward Browne, a great traveller, son of Sir Thomas Browne; Hans Sloane, whose collections and fortune founded the British Museum; Richard Morton, whose Phthisiologia published in 1689 recognizes the identity of scrofula and tubercle, and who was one of the first English authors to lay stress upon the contagiousness of phthisis; John Hawys, a name perpetuated in dispensary work to-day; Samuel Garth, the physician poet of the Kit Kat Club; Walter Harris, whose treatise on acute diseases in infants was the authority for a century; Martin Lister, William Cockburn, who first

[1] Presented at a Joint Symposium of the Pathological, Clinical, Social Work and Administrative Sections at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 3, 1937.

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located the seat of gonorrhoea in the mucous glands, and who wrote a treatise on the diseases of sea-faring people; John Colbatch, a former apothecary who extolled a vulnerary powder and hot water in the treatment of wounds and haemorrhage; William Briggs of Norwich, a pupil of Vieussens and superintendent of St. Thomas' Hospital, who wrote an Ophthalmographia (1676) much praised by Newton; Edmund King, who in 1665 transfused blood directly from vein to vein; Walter Charleton, Collins and Gibson who wrote on anatomy and other subjects; Gideon Harvey, physician to Charles II and William III, Medical Director of the Army in Flanders (1659), City physician of London, who wrote "The Art of Curing Diseases by Expectation" (1689), and whose "Morbus Anglicus" (1672) contained splendid plates of the gross appearance of tubercles and tuberculous disease, considered by Osler quite superior to much of that appearing in our modern textbooks.

In Canto VI of the poem when Carus is chosen by Machaon to go to the Elysian fields to interview the shade of the immortal Harvey, he visits the lower regions where "those Furies wait which execute the harsh Decrees of Fate;" Febris is first, the relentless Hagg with parched Eyeballs, Hydrops, loathsome Lepra and meager Phthisis. Behind these stood the lesser Furies. His description of consumption is terse.

> Whilst meager Phthisis gives a silent blow,
> Her Stroaks are sure; but her Advances slow,
> No loud alarms nor fierce assaults are shown;
> She starves the Fortress first, then takes the Town.

The spirit of service which characterized this first dispensary has been a continuing element through the whole of the history of the growth of the movement.

One hundred years later (1801) John Coakley Lettsom reported that the five London Dispensaries relieved 50,000 poor persons annually, one third of whom were attended in their homes. By 1850 there were 35 dispensaries in London.

There were no dispensaries in the United States until after the Revolution but within a few years the Philadelphia (1786), the New York (1790), and the Boston (1796) were started with the same benevolent desire to relieve the sick poor. These were the three general dispensaries in the United States at the beginning of last century; in 1900 there were about 100. Early in this century forces came into play which materially altered the old dispensary, and developed special dispensaries or clinics for special diseases.

With a full session of this annual meeting devoted to the Tuberculosis Dispensary, opportunity is offered to pay tribute to the pioneer in this field of medicine. Five years ago we celebrated the fiftieth anniversary of Koch's discovery of the tubercle bacillus. Two years ago we met at Saranac Lake to honor the memory and achievements of E. L. Trudeau, the pioneer in the sanatorium treatment of tuberculosis in America. This year, 1937, marks the fiftieth anniversary of the inauguration of the Victoria Dispensary for Consumption, 13 Bank Street, Edinburgh. There can be no doubt that this was the beginning of the first systematic program for an antituberculosis campaign, and that with Sir Robert Philip rests the glory of the conception and realization of a completed local equipment against tuberculosis. From the outset he invested it with prophylactic agency and made it the centre not only for treatment but for prevention, case-finding, record filing, sputum examinations, home visiting both by the physician and the specially trained nurse, social service in the home, the classification and disposal of patients, and the after-care of discharged cases. It was to be a centre for the diffusion of knowledge relating to tuberculosis.

The program for the dispensary, as outlined by Doctor Philip in 1887, includes:

1: The reception and examination of patients at the dispensary; the keeping of a record of every case, with an account of the patient's illness, history, surroundings, and present condition, the record being added to on each subsequent visit.
2: The bacteriological examination of expectoration and other discharges.
3: The instruction of patients how to treat themselves, and how to prevent or minimize the risk of infection to others.
4: The dispensing of necessary medicines, sputum bottles, disinfectants, and, where the patient's condition seems to warrant it, food-stuffs and the like.
5: The visitation of patients at their own homes by (*1*) a qualified medical man, and (*2*) a specially trained nurse, for the double purpose of treatment, and of investigation into the state of dwelling and general conditions of life and the risk of infection to others.
6: The selection of more likely patients for hospital treatment, either of early cases for sanatoria or of late cases for incurable homes, and the supervision, when necessary, of patients after discharge from hospitals.
7: The guidance generally of tuberculous patients and their friends, and for inquiries from all interested persons on every question concerning tuberculosis.

In outlining this program in his address at Boston in 1908 in a public lecture arranged by the Sixth International Congress on Tuberculosis,

Sir Robert said that while the experience of twenty years had led to modifications and extensions of details no essential change had been found necessary in the program.

That within five years of the discovery of the tubercle bacillus such a program should have been outlined, bespeaks the genius, the organizing ability and professional influence of the man who devised it.

With the dispensary the centre of the attack on tuberculosis Sir Robert built up about it as rapidly as possible what he considered the further essentials of a complete local antituberculosis campaign. Within four years the dispensary was moved from its three rooms on Bank Street and a larger house occupied at 26 Lauriston Place. In 1894 the Royal Victoria Hospital was opened, a sanatorium for early cases. Advanced cases were cared for in the general hospitals. In 1903 the sanatorium was enlarged, in 1905 a School for Tuberculous Children was begun at the Royal Victoria, in 1906 a pavilion for advanced cases by the municipality. In 1907, following the lead of Dr. Hermann Biggs in New York, compulsory notification of consumption was introduced in Edinburgh, a measure which Sir Robert had been advocating since 1890 (introduced in New York in 1893, it was made compulsory in 1897). In the same year there was further extension of sanatorium accommodation, while 1910 saw the inauguration of the Royal Victoria Hospital Farm Colony.

In 1912 the Dispensary acquired the present large and commodious building in Spittal Street, thoroughly equipped with consultation rooms, museum, library, facilities for ambulatory treatment, a small laboratory and full accommodation for teaching.

The year 1922 saw the development of the Southfield Sanatorium Colony situated at Liberton. Here, cases of tuberculosis of all kinds and at all ages are received and treated, there is a school for children, a fully equipped research laboratory, and convalescent patients are employed in useful occupations.

The Royal Victoria Hospital Trust also operates a dairy farm with 120 head of cattle, all tubercle free, and kept night and day in the open.

Following the long famous tradition of the Edinburgh Medical School for thorough undergraduate teaching Doctor Philip early in his scheme made arrangements for regular instruction to students. At first the attendance was voluntary, but so broad and thorough did he make the course that it became an integral part of the curriculum attended by every student.

The visiting nurse was one of the outstanding features at the outset. Her investigations and the famous "march past" of the household, children, parents and all others, mark the beginning of our case-finding in our study of contacts.

A volunteer Samaritan Committee of ladies assisted in those cases where financial aid was needed whether for food, clothing or shelter. To this committee also were referred for suitable employment those patients fit for some effort but unable to work an entire day. Years before we began to take up rehabilitation and reëmployment at all seriously, Sir Robert had his dispensary organized for this highly specialized work, caring for both the purely dispensary case and those discharged from hospital or sanatorium. The social reports on living and working conditions were studied as thoroughly as were the medical histories and examinations. The result was a mass of useful information as to the relation of tuberculosis to housing conditions, sanitation, overcrowding and frequent removals, while the plotting of cases on the city map revealed the frequency of the disease in certain houses and streets.

Nor is it to be forgotten that Doctor Philip built the Royal Victoria Hospital near the gates of Edinburgh, not out in the hills or mountains. His results have shown that a sanatorium so placed can be used for teaching the subject of tuberculosis to students and practitioners, be a constant demonstration of methods to a great population and, at the same time, be inferior in no respect to those with presumably better climatic conditions, and far from the patient's home and family.

The advantages arising from Doctor Philip's plan were slowly and gradually recognized elsewhere and it became known as the Edinburgh Scheme. Visitors from other lands came to observe and study it as the most practical and valuable plan for the local eradication of tuberculosis. Standing out in bold relief was this central dispensary, gathering through its work extensive information as to the extent and locations of tuberculosis in the city, and gradually developing about it institutions to care for the cases uncovered through the follow-up of cases, home investigation and the examination of contacts.

In Germany on the other hand the great interest in the erection of sanatoria in the eighties and nineties resulted in other antituberculosis agencies being neglected. The Edinburgh Dispensary received little notice until the Prussian Education Board drew attention to the useful working of the Lille Tuberculosis Dispensary founded by Calmette in 1901. In the United States too the sanatorium movement preceded

any generally organized antituberculosis effort. There is no doubt that the constant outcry of the sanatoria for earlier curable cases did much to arouse concerted action, once they had demonstrated that "of the early cases over 75 per cent are curable, of the moderately advanced 15 per cent and of the far advanced scarcely 1 per cent."

Calmette founded his Preventorium Emile Roux (Dispensary) at Lille in 1901 and within four years France had over fifty established. Calmette considered that the dispensary should not give treatment, but a considerable amount of material assistance, while supervising the home conditions of patients and giving instruction as to methods of prevention of spread of infection in the home. The rules laid down by the National Committee of France in 1928 state that the dispensaries are specially charged with education of patients and their families, to give advice on prevention and hygiene, to secure admission of patients to hospitals, sanatoria and other institutions, to cleanse and disinfect homes and personal belongings. Assistance and medicine are to be given only to the poor, but advice to all who may apply. Contacts and observation cases are to return for further examinations as required. In principle no treatment is to be carried out except therapeutic pneumothorax.

In Scotland in 1906 the Local Government Board advocated a national scheme, recommending to all municipal authorities the establishment of dispensaries as the fundamental basis.

In England the last century saw the founding of a number of special hospitals for the treatment of tuberculosis, and these and the great teaching hospitals diagnosed and treated tuberculosis in their out-patient departments, but there was no concerted antituberculosis work. Although Bodington had enunciated his views as to the value of fresh air in tuberculosis in 1846, and special institutions, still extant, began in 1791, 1814, 1841, 1851 and later, the sanatorium movement in the modern sense of the term began about 1898 as in the United States.

The movement spread over the country largely through the influence of the National Association for the Prevention of Tuberculosis (founded 1899) and its local branches. England's present-day plan for national control of tuberculosis has been founded mainly on the report of the Departmental Committee on Tuberculosis (known as the "Astor Report") made in 1912.

This includes essentially two factors, namely: (*1*) the dispensary unit, consisting of tuberculosis dispensaries, with staff of officers and extensive and varied operations for the detection and prevention of tuberculosis

and with the tuberculosis officer as consultant; (*2*) the institutional unit, consisting of sanatoria, hospitals, training colonies, open air schools, etc.; (*3*) to which may be added after-care, and education of the people.

It is pointed out that a tuberculosis dispensary is not a building but an organization, in charge of a specially trained medical officer with assistants and staff. Notification of pulmonary tuberculosis was made compulsory throughout Great Britain in 1912, and in 1914 was extended to all forms of tuberculosis.

It is now the duty of Councils of Counties and County Boroughs to formulate tuberculosis schemes which will include the three factors outlined above. These schemes must be submitted to the Ministry of Health (in Scotland the Board of Health); when formally approved there is a contribution by the State of 50 per cent toward the annual maintenance. The tuberculosis officer is in charge of the work under the medical officer of health. Every tuberculous person coming within the ambit of the dispensary is entered on the dispensary register and kept under continued supervision (being seen by the tuberculosis officer at least once a year) until the patient (a) could be considered "cured", (b) had died, (c) left the district, (d) refused to continue under public medical treatment, (e) was lost sight of. Cases of pulmonary tuberculosis are written off the registers as recovered when the disease has been quiescent for two years and arrested for a further three years, the nonpulmonary when arrest has been maintained for at least three years. In this connection it is informative to note that in the County of Lancaster with a population of 1,821,000 and a tuberculosis death rate of 57 there were 7,404 on the register December 31, 1935. During the year 169 pulmonary and 556 nonpulmonary cases were written off while only 58 of those written off as recovered in previous years were restored. Twenty of these were pulmonary and 38 nonpulmonary. I would recommend a study of the annual reports of the Central Tuberculosis Officer of the Lancashire County Council (Dr. G. Lissant Cox) by all medical officers of health and tuberculosis committees as valuable records of the practical working of a well organized and well officered county scheme.

It is interesting to note that, with little dispensing of drugs and medicines, and the recognition of the primary functions of a tuberculosis dispensary as case-finding, diagnosis, disposition of cases and with the diagnosis requiring an officer well trained as an internist, the Joint Tuberculosis Council in their report for 1932 recommended that the designation Tuberculosis Dispensary be altered to that of Tuberculosis Clinic.

Britain's comprehensive tuberculosis scheme thus allows each municipality or area to devise its own scheme, but this must be approved by the Ministry of Health and we find it based upon the Edinburgh Scheme, with the Department of Health and all its powers behind it. An example is Section 62 of the Public Health Act 1925, which authorizes the local authority to secure the compulsory removal to hospital of any person suffering from pulmonary tuberculosis in an infectious state.

The influence exerted by the Edinburgh System in America is perhaps not realized by the younger members of this Association, who may be interested in knowing something of its effects with us. Dr. Hermann Biggs, in 1911, writing on "Administrative Measures for the Control of Tuberculosis in New York City," said:

I think it may be fairly said that at the present time in Edinburgh and New York more comprehensive and satisfactory plans are actually in operation than in any other cities, although in recent years several of the larger towns of England have put into effect very complete measures. So far as I can learn, to Dr. R. W. Philip and to Edinburgh belongs the great credit of having very early appreciated the significance to the whole tuberculosis movement of the special tuberculosis dispensary, and of having really initiated the movement for the control of this disease by the establishment of a special institution in that city.

It was a long time before the example of Dr. Philip in this respect was followed. Commencing with this special dispensary, and working with untiring energy and unbounded enthusiasm, directed by an unusually far-seeing and intelligent conception of the significance and scope of the work, Dr. Philip and his co-workers gradually elaborated a comprehensive scheme covering all the phases of the problem. In this work their voluntary efforts have in recent years been supplemented by the co-operation of the sanitary authorities, who have provided for notification and registration, the disinfection of premises, and the other necessary preventive measures.

In New York, as I have previously pointed out, the procedure has been quite different, but the resulting plan, which is now in effect, is not unlike that of Edinburgh.

I regard special tuberculosis clinics or dispensaries as constituting the initial step and a fundamental part of any successful scheme for the prevention of this disease. The importance of this was first recognized in Edinburgh.

Where such a comprehensive scheme as has been outlined in part can be made effective, in my judgment there is every reason to look forward for a steady and continuous reduction in the morbidity and mortality rate from this disease.

William Charles White has written:

Up to January 1906 practically no step had been taken in the effort to reduce the incidence of mortality from tuberculosis in the city of Pittsburgh, U. S. A. At this time a group of business men banded themselves in a unique organization to effect some struggle against this infection.

In my early conference with this group of men I found that their desire was to move Pittsburgh from the position of a negative factor in this phase of public health work, to accomplish this in a business-like way, and to give the director a free hand in the development of the different factors of an organization necessary to accomplish this purpose. For some years I had been familiar with the plan which has been inaugurated, successfully operated, and preached by Dr. Philip. This plan may be briefly stated as the correlation of all factors active in the tuberculosis crusade in some centralized system for the municipality or district in which these factors are operative, or, to emphasize the other end of the scheme, the municipal or regional supremacy in tuberculosis work through a centralized correlated system of all operative factors. The great common sense of this plan at once impressed me, and its application to Pittsburgh appeared a great opportunity. The more I have laboured in this field the more I am impressed with the fact that in this idea lies the secret of successful control of this sickness, and it is a great pleasure to do honour to Dr. R. W. Philip, who first suggested it and has so perfectly developed and operated it in Edinburgh.

May I also recall the fact that at the Washington Congress of 1908 Doctor Philip was presented with a map of the state of Pennsylvania showing sixty-seven dispensaries marked on it, all on the lines of his dispensary in Edinburgh and all founded within the space of three years.

In the United States and in Canada each state or province deals with the health of its people and would seem to be responsible for the control of tuberculosis within its borders, and there is no nation-wide scheme for the dispensary control of tuberculosis as in Great Britain. A study of Tuberculosis Clinic Practice in the United States is presented to this annual meeting as a result of a clinic survey by the Committee on Clinic Standards. From this report it is seen that there were relatively few clinics before 1900 and that most have been established since 1920; that they are conducted by various official or nonofficial agencies, and that their principal purpose is the diagnosis of tuberculosis. Relatively few are equipped with X-ray apparatus, though many have such conveniently available, but educational work is carried on by most of them, and visiting nurses are generally available to supervise patients in their

homes. Some states are well provided with clinics, New York and Pennsylvania having more than one hundred, while at the other extreme we are told that four states have none and four others only a single permanent clinic in each. About one-half of the states have traveling clinics in addition to the permanent units and these traveling units are operated about one-half by state agencies and one-half by local agencies. About one-fourth of all the clinics reported pneumothorax treatments being given, and two-thirds of these undertake inductions. About 23 per cent of all the chest clinics are attached to hospitals or sanatoria.

Doctor Philip's visit to the 1908 Congress was responsible for great advances in antituberculosis measures in Canada. On the invitation of the Canadian Tuberculosis Association, Doctor Philip on his way to Washington visited among other Canadian cities, Montreal and Hamilton. In Montreal he addressed the Board of Trade at a luncheon meeting giving a memorable address which so powerfully impressed one of the leading citizens present that he attended the meetings of the Congress, met and discussed methods with various workers there, visited the dispensary at the Johns Hopkins Hospital and the Phipps Institute in Philadelphia, and on his return converted an old mansion in the heart of the city into a dispensary which became the Royal Edward Institute. Its doors were opened the next year by King Edward VII through cable connection from West Dean Park, Chichester, England, with Sir Robert Philip present as an honored guest. It was named for his Majesty, the Royal Edward Institute. This Institute now in close affiliation with McGill University, and the Bruchesi Institute in similar relation to the University of Montreal are potent factors in Montreal's antituberculosis campaign.

Sir Robert's part in the Hamilton scheme is thus told by Doctor Holbrook in his "Story of the Hamilton Health Association":

> The most important step in the history of the Mountain Sanatorium was probably the result of the visit to Hamilton in 1908 of Dr. Philip of Edinburgh. While he praised us for the start we had made, the most valuable idea that he left was this, that in his plan of organization the chest clinic should be made to function as the centre, or as he called it "the clearing house" for all the work of the organization. As a result a house in the city was bought and fitted up as a clinic. This became the headquarters of the visiting nurse, and gradually the work increased until at length the quarters were hopelessly out-grown. Two years ago, it was possible to persuade the Board of Health to recognize their responsibility for this work which should be a part of any programme for

the prevention of disease, by furnishing us with new quarters. This resulted in the establishment of an up-to-date Health Centre in Hamilton.

Even with Dr. Philip's advice we were slow to appreciate the importance of the clinic as anything more than a place for chest examinations, though, as time passed we gradually learned that better co-operation was secured by trying wherever possible to send to some interested person a report on each case examined.

The chest clinic is a part of our work that we are striving continuously to improve and extend for we have come to believe that very much of the credit for our low death rate should go to this department of our work.

This appreciation of the value of the dispensary or clinic in tuberculosis control has greater force when we add that the city of Hamilton with a population of 160,000 has lowered its death rate from tuberculosis to below 30 per 100,000.

The dispensary as a voluntary health organization, through its discovery of cases by examination of contacts of those cases coming under its care, brought to the public attention the need for beds for treatment and for provision for after-care and continued supervision of those who had completed treatment. With the enactment of compulsory notification of all cases it became essential that there should be the closest co-operation between the voluntary dispensary and the medical officer of health who received these notifications. These notifications demand, for any proper degree of control, that investigation of the patient's home and family must be carried out either by a well organized health department with its physicians and visiting nurses, or turned over to the dispensary of the area for the necessary investigation. In other words there must be a decision whether the file of registered cases is to be kept up by the Medical Officer of Health or delegated to the dispensary, the dispensary in all cases being the agent for examination, diagnosis and for recommendation as to disposal of the case, whether for hospital, sanatorium, home care, or further observation. An effective campaign requires the directed efforts of public health administrative machinery, and where this is lacking or deficient, the results must be unsatisfactory for control is not complete. In our cities and the more densely populated rural areas there is usually a full-time health organization with nurses and other staff requisite to report, record and follow up. Special tuberculosis dispensaries or clinics, or chest clinics in the larger hospitals offer the diagnostic and consultation services necessary for the demands of the health department. But in the sparsely settled

areas there may be only a part-time health officer with no clinical or nursing staff. For these areas we have seen in recent years the development of the traveling clinic, which at fixed or irregular intervals will visit certain towns or districts, having previously notified the district officer of health and all practising physicians. An endeavor is made to have in attendance (a) all known or reported cases of tuberculosis, (b) all contacts, (c) all for whom the laboratory has reported positive sputum if not yet notified, (d) all ex-sanatorium patients for check up, (e) all patients for whom the family physician wishes consultation, that is, doubtful or suspect cases.

In the Province of Manitoba (population 711,000) the traveling clinic began in a small way in 1926 with 170 people examined. The next year six centres were visited and 658 examined. In three years of 2,665 examined 11 per cent were found to have clinical tuberculosis and of these 231 were new discoveries. These clinics have grown until now about 5,000 examinations are made each year, about one in seventy of the rural population. About 11 per cent of those examined have tuberculosis. Excluding the ex-patients and other known cases nearly 7 per cent of the contacts and suspects examined were found to be tuberculous. Of over 6,000 examined and X-rayed, about 10 per cent had clinical tuberculosis. There is a steady decrease in the number of new discoveries each succeeding year in localities where a yearly clinic is held.

A further development has been the carrying on of fixed clinics at intervals of one to four weeks, in neighboring towns and counties by the staff of the sanatorium in the district. These offer excellent service not only for discovery of new cases but for follow-up of discharged cases.

Traveling diagnostic clinics were instituted in the Province of Ontario in 1930 when 1,204 persons were examined. The work has grown until in 1936 8,856 persons were examined, of whom 15.4 per cent were found to have tuberculosis. An attempt is made to examine all contacts of known cases in the districts visited. The Director of the Division of Tuberculosis Prevention in a recent paper emphasizes the importance of the examination of contacts in his statement that

> In 1935 54% and in 1936 53% of newly discovered cases (including the childhood type) had disease in the minimal stage, as compared with approximately 40% in the early years of the traveling clinic work. In 1936 72% of new cases discovered (all types) gave a history of contact. Of those newly discovered cases classified as minimal, 50% were referred because of contact only and gave no history of symptoms suggestive of disease. Of those newly-discovered

cases classified as moderately advanced 35% were referred because of contact only and gave no history of symptoms suggestive of disease. Forty-seven per cent of all newly discovered cases (all stages) in two clinics were referred solely on account of contact. These findings establish the value of contact examination in the absence of symptoms and show that one-third of those patients with moderately advanced disease were not conscious of ill health.

In the Province of Ontario, population 3,596,000, the death rate has fallen in 50 years from 125 to 36.2 per 100,000.

In the early days of the dispensary, domiciliary treatment and supervision was a necessary part of its work. With the provision of hospital and sanatorium beds, every patient in the infectious state was removed from home if possible, and dispensary treatment practically ceased. In France, as noted, the dispensary at its inception did not treat patients and this became a rather general practice except for those patients who must remain at home. Sanatorium treatment with rest in bed was our only valuable therapeutic measure, and this was beyond the scope of the dispensary. The world-wide adoption of pneumothorax therapy has brought up again the place of the dispensary in treatment, and this was one of the subjects for discussion at the International Union at Warsaw in 1934. In the opening paper Léon Bernard pointed out that there was no Act in Germany, France or Great Britain which precluded the use of dispensaries for therapeutic purposes, and expressed the opinion that pneumothorax therapy should be carried out in the case of the poor and for those referred by physicians. He reported this to be the practice in 19 out of 25 countries, and in France that about one-half the dispensaries undertook such treatment. In Denmark it has not been found necessary for the dispensary to undertake this work, as the sanatoria and hospitals are so situated as to be available for patients living at home. In Poland, in 1933, 75 dispensaries were doing refills, and others were training their physicians in the procedure that the practice might be extended. In Great Britain the dispensary, now a pivotal point in a great national organization, is being equipped with the necessary X-ray and other equipment for pneumothorax therapy. In some, inductions are done as well as refills. One of the representatives at the Union from the United States expressed himself as enthusiastic in adding pneumothorax therapy to the program of the dispensary, going so far in his enthusiasm as to say (I quote) "The sanatorium of the past, although accredited with creditable achievement will gradually find, largely because of economic conditions, that the salubrious climate of the seashore or mountain top will

give way to the preventive, economic, easily supervised method of clinic control of tuberculosis."

In the Soviet Union we are told that the dispensary is the centre of the campaign against tuberculosis, and that artificial pneumothorax (unilateral and bilateral) occupies the first place among the methods of ambulatory treatment in the dispensaries, and there is no hesitation in induction when the patient cannot be placed immediately in a sanatorium or hospital.

One of the speakers at the Congress struck a warning note in pointing out that with therapy becoming an important department of the dispensary there is grave danger of easing up on its prime objects, prophylaxis and early case finding.

The evolution of dispensary control of tuberculosis has not been along lines of principles but rather of the adoption of all newer procedures in diagnosis and treatment, in notification and follow-up, closer coöperation with health departments and in the development of the traveling clinic. The Mantoux test has become an important addition to the "march past," the X-ray has become an indispensable aid in diagnosis allowing us to see tuberculosis where it could not be heard, the examination of all contacts by these additional methods of study has resulted in discovering many more cases in the earlier curable stages, the awakening of our health departments to the value of the dispensary in discovering preventable disease in a curable stage and in the prevention of further infections has made the dispensary a more potent factor in prevention, the adoption of pneumothorax therapy as a dispensary procedure has still further lessened the spread of infection, while the development of the occasional and traveling clinic has extended enormously the possibilities of dispensary control.

The isolated clinic has its value in the diagnosis of tuberculosis, in placing the patient under proper treatment and supervision and lessening the dangers of infection; and segregation will always be an important aid in disease prevention but no clinic or dispensary can serve the health needs of its area without the closest coöperation with the health department, and this, of course, must be well organized and competent in order to receive the best results possible from coöperation.

The dispensary scheme as outlined by Sir Robert Philip fifty years ago has demonstrated its value. Its basic principles are unchanged. No better scheme has been propounded; it has been the means of lessening

the ravages of a preventable disease. Sir Robert's scheme shows the Medical Officer of Health as an integral part. Edinburgh, New York, Framingham, Cattaraugus County, have taught us what can be accomplished by organization and coöperation. "The key to complete success in the campaign against consumption lies in the harmonious co-ordination of well directed measures."

CLINIC STANDARDS AND CLINIC PRACTICE[1]

HERBERT R. EDWARDS[2]

Fifty years ago Sir Robert Phillip established the first tuberculosis clinic at the Royal Victoria Dispensary, Edinburgh. Since that time, there has been a steady growth in the number of tuberculosis clinics throughout the world. In the United States to-day there are approximately 1,000 clinic services in operation. The cost of these services is conservatively estimated at between seven and eight million dollars per year. There is evidence to show that the number of such services should be increased and that the standards of practice should be raised to higher levels.

During the past few years every official and voluntary health agency budget has been carefully scrutinized, with a result that many have experienced a revision downward. This experience, as distressing as it may have been, has nevertheless been desirable because it has forced us to take stock of our resources, our methods and practices, and to weigh them in the cold light of fact. Biggs has stated that Public Health is purchasable. With a specified sum one may expect to accomplish a certain result. Generally speaking, we have been far more concerned with the securing of a theoretical per capita health budget based on existing methods than we have with the analysis of those methods to ascertain their effectiveness. We have reached the point in tuberculosis control where we can no longer continue to accept blindly many of our more or less established practices. There is a growing amount of evidence that some of these practices are excessively expensive compared with their efficacy. That we should have progressed this far in tuberculosis work without more attention to the effectiveness of our program is a sad commentary on the whole movement. With the enormous volume of clinic service rendered in this country in any one year we should,

[1] Presented at a Joint Symposium of the Pathological, Clinical, Social Work and Administrative Sections at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 3, 1937.

[2] Bureau of Tuberculosis, Department of Health, New York City.

with proper controls and supervision, have been able to arrive at more definite conclusions.

It is fair to state that during the past fifty years we have not had any generally accepted standards of clinic practice. From time to time there have been monographs on the subject but little has been done to secure their general acceptance. All available material on the subject is now somewhat out of date. There has been, however, a constant demand for a set of minimum standards by those clinics now in operation as well as by those agencies anxious to open new services. In 1934 the National Tuberculosis Association appointed a committee of five to study the problem and submit a clinic manual indicating minimum standards of practice.

First, the Committee had to ascertain the number, type and general policies of existing clinics. All existing material was completely out of date; accordingly, the first step toward a survey was the making of a new census. The National Association through its state and local affiliated associations assisted in the collection of these data within their respective districts. A questionnaire form was prepared which attempted to cover the major factors involved in clinic practice and material of such a nature that it could be readily tabulated and analyzed. These data have been prepared and were made available to the committee early in 1937.[3]

This study revealed some rather amazing facts. There were approximately 1,000 clinics listed, although only 639 gave sufficient detailed information suitable for incorporation in the final analysis. For the most part the study deals with the permanent clinic, although we did secure much data from the itinerant and occasional clinic.

From these data we are able to deduce a few generalizations that will indicate the volume of service rendered. It is estimated that the 1,000 clinics held 100,000 clinic sessions during the year. There were about 2,500,000 visits made by patients during these sessions, or an average of 25 visits per clinic session. Unfortunately, only a few clinics indicated the number of individuals making these visits, although such information is pertinent to the proper appraisal of clinic service. We have estimated that 1,000,000 individuals made an average of two and one-half visits each.

The combined visits to the homes of patients by clinic personnel and others were estimated to be over 3,000,000 for the year.

[3] The committee was composed of the following members: Herbert R. Edwards, Chairman, Vera V. Norton, H. S. Spector, M. F. Haygood and Arthur DeWees, Secretary.

DIAGNOSTIC SERVICES

In diagnostic services rendered to the patient, three of great significance stand out. There were between 500,000 and 600,000 sputa examined, a ratio of one sputum examination for about each two individuals visiting the clinic. There were approximately 600,000 X-ray films used, a ratio of one film for each 16 individuals visiting the clinic. If one X-ray film of each patient is considered desirable for good clinic practice, then it is quite obvious that such a practice is far from universal, to say nothing of the number of serial films desirable in the routine follow-up of cases. Yet, according to the survey practically all clinics reported X-ray equipment or easy access to the same.

The tuberculin test is a well tried and supposedly a generally accepted diagnostic aide in the examination of children. Yet in the 572 permanent clinics there were 29 which did not use it, and 19 in which it was used only occasionally. In the case of adults, the number of clinics not using tuberculin was much higher. It is hard to believe that intelligent modern methods of tuberculosis practice exist in these clinics. If we analyze these clinics from the standpoint of the sponsoring agency, the result is the more perplexing and there seems to be even less justification for it. There were 11 clinics under State Departments of Health, 10 under local health departments, 12 under local tuberculosis associations, 7 under tuberculosis hospitals and sanatoria and 7 were under other public or private agencies. All of the 30 itinerant clinics, except one, used tuberculin in the diagnosis of children. Six of the 37 occasional clinics reported nonuse of tuberculin.

TYPES OF CLINIC SERVICE

The tuberculosis clinics operating in this country are predominantly of a permanent type. Of the 639 analyzed, 572 were permanent, 30 were itinerant and 37 were classified as occasional. In all three groups, the greatest expansion has been since 1920, and from additional facts reported it is obvious that there will be a further expansion in the coming years. The major activities were concerned with diagnosis, consultation and treatment. It was of interest to note the increasing use of pneumothorax in clinics. With the exception of three itinerant clinics, all pneumothorax work was done in permanent clinics, many of which were connected with hospitals or sanatoria. In 111 of the 169 permanent clinics, it was indicated that initial pneumothoraces were given as well

as refills. For the most part, these clinics were affiliated with hospitals or sanatoria where such a procedure might be acceptable.

There is a growing tendency to expand this type of service to meet the problems presented by the shortage of sanatorium beds and the urgent need for prompt treatment of cases. It is a well known fact that some competent physicians have initiated pneumothorax in their office or in a clinic without disastrous results. However, it hardly needs arguing to state that such a policy, for the average clinic, would be frought with serious consequences. The best medical judgment demands that such work is by rights a hospital job.

DIAGNOSIS AND SUPERVISION OF CASES

The first function of a clinic is to make a diagnosis. The scope of diagnosis should be all inclusive. It is not enough to-day to stop with "tuberculous" or "nontuberculous." There are many nontuberculous pulmonary lesions of vital importance as far as the patient is concerned that should be diagnosed. Thousands of these cases have passed through our clinics in the past undetected. It is encouraging to note the improvement in the diagnosis of such conditions within recent years. Thus it is of interest that 133 clinics used lipiodol regularly and 22 occasionally. The use of the bronchoscope was not indicated in our questionnaire forms.

The promptness with which the original diagnosis is made will determine in large measure the success of the clinic as well as its standing in the community. It is not uncommon to find in the case files of many clinics a large number of undetermined or suspicious cases whose diagnosis has not been completed. Usually this is the result of placing too much dependence on the physical methods of diagnosis such as auscultation and percussion. The rush of work in our modern clinics is usually so great that the physicians' acuity of hearing is seriously handicapped, and rather than miss a possible case he diagnoses it as suspicious and and indicates a revisit hoping that at the next session he will have more time to complete the diagnosis. Experience shows that a large number of such cases never return and many require an unreasonable number of nursing visits to the home to secure coöperation. All the while these records accumulate and clutter the file. They represent loss in efficiency and dissipate thousands of nurses' visits and that in turn is a waste of our limited resources.

Much of this difficulty could be eliminated if the case were routinely

X-rayed at the time of the first visit. An X-ray study should be an essential part of each primary examination. In the event that the patient fails to return as requested, a reading of the X-ray film would be ample evidence in many instances for discharging the case. In our experience in New York City with this method we are finding it a great saving and we believe it creates in the patient more confidence in the clinic.

The prompt diagnosis of the new case would solve much of our problem in later clinic supervision. The length of time necessary for case supervision constitutes one of the most perplexing problems of the clinic. In some clinics an attempt is made only to arrive at a diagnosis. No permanent clinic should be operated for this one purpose, unless it might be a consultation chest service for the private practitioner where the patient is immediately referred back to his doctor for further supervision. In other clinics, an attempt is made to carry every diagnosed case, as well as contacts, for an indefinite period. This plan tends to accumulate an excessive case load, for many of these cases little is done, and for many there is no real need of repeated examinations. The system can result only in inefficiency.

It is believed that the real responsibility of the clinic in such matters is to render intensive supervision both to the active or potentially active case during the period when such care is necessary, and also to the contact case during that period when one might logically expect a lesion to develop. In any event, it is difficult to establish a routine that can be applied with justice to all cases. In this matter, there is nothing that will replace common sense and medical judgment.

In New York City, we have found it of value to divide our clinic file sharply into "active" and "inactive," the designations having nothing to do with diagnosis or clinical symptoms. In the active file, we carry all diagnosed cases, contact cases, and cases needing further observation. In such cases a return is scheduled for any period up to six months. In the inactive file are placed all negative, arrested and other cases needing no further examination. It is our feeling that a case in need of continued supervision should be seen at least within six months. While this is an arbitrary division, it tends to make our clinicians appraise their cases more carefully. Furthermore, it keeps before the clinic and district nurse our acute problems rather than a hodgepodge of all cases, many of which are in no need of attention. It has been our practice to discharge from supervision any pulmonary case that is adjudged as arrested ac-

cording to the standards of the National Tuberculosis Association. Here again we judge individual cases. None of our rules and regulations are expected to interfere with the best judgment of the clinician, and we do not believe that many cases are placed in jeopardy by this plan. Furthermore, the volume of work in our clinics will not permit the carrying of all cases for indefinite periods. It is believed that the problem is not essentially different in most other clinics.

In the case of contacts, we have made certain generalizations which we feel are valuable in determining the length of supervision.

1: Children under five should be supervised for a time sufficient to indicate by X-ray that no lesion exists, usually until seven years of age if the source of infection has been removed. In the presence of a source of infection or a recently quiescent or arrested lesion, supervision should be continued if possible into young adult life, that is, twenty five years.
2: Adolescents and young adults (12 to 20 years) with exposure to patients with positive sputum within two years, reacting positively to tuberculin, regardless of the X-ray findings should be supervised until their twenty-fifth year.
3: Adolescents and young adults with questionable or minimal lesions with no history of exposure for the previous two years should be supervised until their twenty-fifth year.
4: Where the source of infection has been removed, all contacts who are negative to tuberculin for a period of at least three months after such removal are to be discharged.

UNDERSTAFFING OF CLINICS

There is a definite relationship between the number of physicians at a clinic session, the number of patients examined and the quality of service rendered. In 394, or 69 per cent, of the permanent clinics a single physician was in attendance. If the average session attendance can be estimated at 25 as previously shown, then it follows that the service rendered can only be of a superficial character for new cases are included in the total attendance. In New York City, in 1936, 82,280 individuals were treated, 31,612 were new cases, making a ratio of one new case for each 2.6 individuals examined. In a permanent clinic one may estimate new cases as 34 per cent of the attendance, which require extra time and attention. While the survey did not clearly indicate the degree of understaffing, it is nevertheless an acute problem in many clinics. It is believed that a physician should not be expected to handle more than fifteen cases at a three hours' session, including new cases and revisits.

Longer sessions tend to blur the acuity of his perception and, at best, he has practically no time to make proper notations on his records and consult with the patient.

PERSONNEL QUALIFICATIONS

The success of the clinic will in the final analysis depend upon the calibre of the personnel. The finest appointments and plant are of little value if the personnel is not well trained and possesses a pleasing personality. Tuberculosis, being a chronic disease requiring long periods of supervision, demands a much greater degree of tact and understanding from the physician than many other types of diseases. The type of reception offered the patient at the time of his first visit to the clinic will determine largely his willingness to coöperate in the future. The same may be said for the nurses' attitude in the home. An unsympathetic or unintelligent home visit only tends to build up a sales resistance on the part of the patient to subsequent visits.

The physicians working in the clinic should be well grounded in their knowledge of chest diseases. It is no longer sufficient to have any practitioner assigned to this work. Fortunately, there is now an increasing body of physicians available for such service who have had special residencies or courses in tuberculosis and chest diseases. It is vitally important that the clinic physician have some connection at a hospital or sanatorium where chest conditions are handled. Such contacts are stimulating to the physician and frequently assure a continuity of service for the patient as he may remain under the same physician in both the clinic and sanatorium. This relationship has been well developed in those communities where the hospital or sanatorium staff is responsible for the clinic service as well. This management is of greater value when the physician is a full-time paid employee of the sanatorium.

The physician serving in a clinic should be paid for his services. In the clinics surveyed the average pay per session was about $3.00. This is a small amount and cannot be considered adequate for the quality of service rendered. However, some payment does serve to place more responsibility on the physician, and he is more likely to be prompt in attendance and remain until the work is finished. Full-time pay for clinic service is out of the reach of most clinics and it is probably not desirable unless the physician has an active hospital connection in addition.

NURSING SERVICE

The clinic could not function long without a nursing staff. It is the nurse who knows the case, his family and his problems. The permanence of her appointment is directly related to the success of the clinic. The patient looks more to the nurse than the doctor for advice, for it is so frequently the nurse who really gets across the recommendations made by the doctor. Ideally this should not be true, but nevertheless the rush in the clinic often prevents the physician devoting the necessary time to each case.

In the majority of clinics studied it was found that the clinic nursing staff was responsible for the home visiting as well. There are communities where such service is rendered by outside agencies such as visiting nurse associations. The former is perhaps best because it will mean a more intimate knowledge of clinic experience which can be more satisfactorily translated to the home conditions, and the reverse is equally true. In those communities where the nursing service is under the public agency and the field nurse has the same position as the visiting nurse association, the problem is the same. Frequently these services are generalized in character, meaning that tuberculosis is only a part of the job and one which is frequently deferred when other acute emergencies arise. This deflection of activities is bad enough, but it is also frequently found that the nurse is not well trained in tuberculosis work. There is no logical reason for such conditions to exist, and in most instances the responsibility may be squarely placed at the door of the tuberculosis service. The reason that many nurses do not render a good tuberculosis service is because they have not had proper training and therefore do not understand the problem. A series of courses in tuberculosis, including a historical sketch, the pathogenesis and epidemiological aspects and the day-by-day problems in the field, can always be arranged and will be readily attended by the nurse. In addition to formal lectures, provision should be made for small group conferences where the clinic physician and nurse can get together and discuss the many problems that baffle both. Any administrator who will take the time to apply himself to this problem will quickly appreciate its potentialities.

EDUCATIONAL ACTIVITIES

The tuberculosis clinic should be an educational institution for professional groups. The variety of material passing through the average

clinic is little short of phenomenal, seldom has it been completely worked up for presentation. One will see practically every type of pulmonary lesion in the course of time. Some medical schools have appreciated the value of this opportunity and to-day 37, according to the survey, have some type of tuberculosis clinic connections. There are hundreds of other clinics, however, that are not using their facilities for teaching purposes. In the survey of clinics, 253, or 40 per cent, reported that the clinic was used as a teaching centre. We have never made a sufficient attempt to utilize our clinics as teaching centres for the private practitioner. He can be one of the most important cogs in our case-finding efforts if sufficiently aroused to his opportunity. Abundant material of great interest is readily available; it only awaits the interest, initiative and enthusiasm of the clinic physician to put it together in a palatable form that will be readily grasped by the private practitioner.

CLINIC LOCATION AND AFFILIATION

The location of the clinic is of considerable importance. Primarily it should be conveniently accessible to the population to be served. The ideal location, providing the foregoing needs are met, would be in connection with the outpatient department of a general hospital or a sanatorium. A close affiliation with other polyclinical medical and surgical services is of the greatest value, for there are few cases attending our tuberculosis clinics that are not in need of other specialistic services. This arrangement unfortunately is not available for all clinics. In some of our larger cities, the location of the hospitals and the area to be served are so far apart that such a plan could not be conveniently arranged. There is also the problem of transportation, and in many general hospitals where such a service could be rendered there is a lack of interest if not real resistance on the part of the staff to develop a chest service. This attitude is gradually disappearing, due quite largely to the growing interest in chest diseases in general as compared to tuberculosis. It is hardly necessary to say that where such facilities are not available under the same roof there should be some arrangement whereby the patient could be referred for diagnosis and care for conditions other than tuberculosis.

CLINIC SPACE AND EQUIPMENT

Few of our clinics are housed in adequate quarters in consideration of the service rendered. A permanent clinic should have sufficient floor

space to permit reasonable comfort for both staff and patient; privacy for the patient and at least a quiet examining room for the physician. In addition to the usual clinic furniture, files, etc., there should be at least a fluoroscope arranged conveniently to the examining rooms. If pneumothorax refills are administered, a fluoroscope is absolutely essential.

A radiographic unit should be included in the clinic plan, or at least be readily available, so that X-ray films may be obtained at the time of the initial examination as well as during the follow-up period, so essential in good case management.

Laboratory facilities for sputum examination may be located at the clinic or readily accessible to it. The routine should include direct smears, concentrates, and cultures in selected cases.

Facilities for routine nose and throat examinations and for bronchograms are desirable.

The foregoing equipment will permit adequate diagnostic and supervisory service for most problems in tuberculosis and chest diseases. Bronchographic and other special work will be done best in a hospital.

CONCLUSIONS

There are over 1,000 tuberculosis clinics in the United States. The volume of service rendered and the cost of it has reached the point of a big business enterprise. The practices in these clinics vary widely even in such commonly accepted diagnostic criteria as X-ray, tuberculin and sputum examinations. It is obvious that the time has arrived when we must formulate more definite standards of practice in diagnosis and supervision.

TUBERCULOSIS CASE-FINDING IN A CONSULTATION CHEST SERVICE FOR PRIVATE PHYSICIANS[1,2]

ISRAEL STEINBERG AND MARGARET W. BARNARD

This paper presents a critical analysis of a chest consultation service for private physicians as a tuberculosis case-finding procedure. Such a service not only assists the physician in the accurate diagnosis and proper care of tuberculosis patients, but also differentiates and diagnoses other chest conditions. The data here presented are from the records of the Chest Consultation Service maintained by the Department of Health of the City of New York at the Bellevue-Yorkville Health Demonstration (now the Kips Bay-Yorkville Health Center).

The private physician, and more particularly the general practitioner, has a unique responsibility in preventive medicine. His clientele in general consists of persons with modest incomes who seek neither free clinic service nor, at least in the beginning of an illness, the services of specialists. As he is often the first one to be consulted, he must be aware of the many possibilities and alert to give proper guidance to these patients. Thus in the control of tuberculosis there is opportunity for the private physician to become an important "case-finding agency."

Recognizing the potentialities in this field, the Health Department of the City of New York, in 1929, under Dr. Shirley W. Wynne, then Commissioner, with the coöperation of the Bellevue-Yorkville Health Demonstration, opened the first official Chest Consultation Service for Private Physicians.[3] The objective was to place at the disposal of the private practitioner certain services necessary for the diagnosis and control of tuberculosis, which were not at his immediate command and for which the patient would be unable to pay the fees of specialists. Only patients who presented a letter from a private physician were admitted. These services included:

[1] Presented at a Joint Symposium of the Pathological, Clinical, Social Work and Administrative Sections at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 3, 1937.

[2] From the Bureau of Tuberculosis, Department of Health, New York City.

[3] The first service of this type in New York City was started in June, 1924. at St. John's Hospital, Long Island City, under the sponsorship of the Queensboro Tuberculosis and Health Association.

1: A thorough history and chest examination by a competent specialist in the field of tuberculosis.
2: X-ray films and fluoroscopic study of the chest.
3: Examination of sputum for tubercle bacilli.
4: Other procedures when indicated, such as bronchograms, urinalysis, or Wassermann tests; and Mantoux tests routinely in children.
5: A complete report within 48 hours to the referring physician of the physical, X-ray, and laboratory findings; the diagnosis or a discussion of the differential diagnosis; the opinion of the consultant as to the proper treatment and further disposition of the case, with practical suggestions as to how this can best be accomplished in the individual instance. In tuberculosis cases, a statement of the importance of contact examination and an offer to examine the contacts by X-ray; an invitation to have the physician come and view the X-ray film and consult about his case.
6: A request for subsequent visits when a final diagnosis is difficult or impossible to make on the first visit. All such returns are made through the referring physician. Frequently, the practitioner returns the patient either for periodical examinations or when he feels that a new development in the case requires further advice.

From the first, there has been stressed the maintenance of the highest ethical relationship between the referring physician and the consultant in charge of the service. Beyond the taking of the history and the necessary inquiry regarding pertinent facts, the case is not discussed with the patient and the private physician is left entirely free to use the report of the consultant as he deems advisable.

That this service met a real need has been evidenced by its immediate and increasing use by private physicians. In the ensuing seven years, nine additional such services have been opened throughout the city and the procedure is an accepted case-finding method in the tuberculosis control program of the Health Department.

Any case-finding plan should be judged in the light of certain fundamental questions.

1: Are the available facilities adequate for accurate diagnosis?
2: Is the group selected a productive one?
3: What are the results in terms of (a) percentage of cases diagnosed tuberculous? (b) percentage of cases diagnosed tuberculous in the minimal stage?
4: Does the establishing of a correct diagnosis lead to proper care from the viewpoint of the patient and the community?
5: Are there defects in the plan and how can they be remedied?

The Clinical Facilities: The staffs assigned to this service have been recognized as well trained chest specialists. The four consultants assigned to this clinic since its beginning have all been or still are on the staff of the Tuberculosis Service of Bellevue Hospital. Thus there has been a uniformity in the diagnostic criteria used by each. For the first four years, during the formative stage, Dr. J. Burns Amberson, Jr. acted as consultant to the service.

The clinic is housed in a health centre with adequate diagnostic facilities. Modern X-ray equipment, sufficient films, and the services of a well trained X-ray technician are available. Electrocardiograms and the opinion of a cardiologic consultant are obtainable, as the cardiac clinic adjoins the chest clinic. The laboratories of the Health Department are available for sputum examinations and other tests. It is believed that these facilities are adequate ior establishing accurately any chest diagnosis which does not require a period of institutional observation.

The Group Selected: The only selective factors governing the admission of patients to this service are: first, that the physician feels that the patient is financially unable to secure such services from private sources (the referring physician being the sole judge), and second, it is endeavored to restrict this servce to those practitioners with offices within the clinic district. The patient may, therefore, reside in any part of the city, the aim being to make the service convenient to the practitioner, who may avail himself of the opportunity to contact the consultant personally and discuss the problems presented in the case. This is an educational service for the practitioner for it gives our consultant an opportunity to discuss the X-ray films, findings and recommendations and plan with the physician the proper disposition of the case, as well as the handling of contacts.

This study covers the work in the clinic for the period 1929–1936. During that time 12,300 individuals were examined. We are here concerned with those in which a diagnosis of tuberculosis was made, a total of 2,119. The race, nationality, occupation, age, and sex were as follows: 97 per cent were white, less than 1 per cent were Negro, and the others scattered among the various races (chiefly Chinese). Of the white group, 57 per cent were native-born. As to occupation, nearly 74 per cent were clerks, domestics, food-handlers, skilled and semiskilled workers. Only a small number, 6 per cent, were in the business and pro-

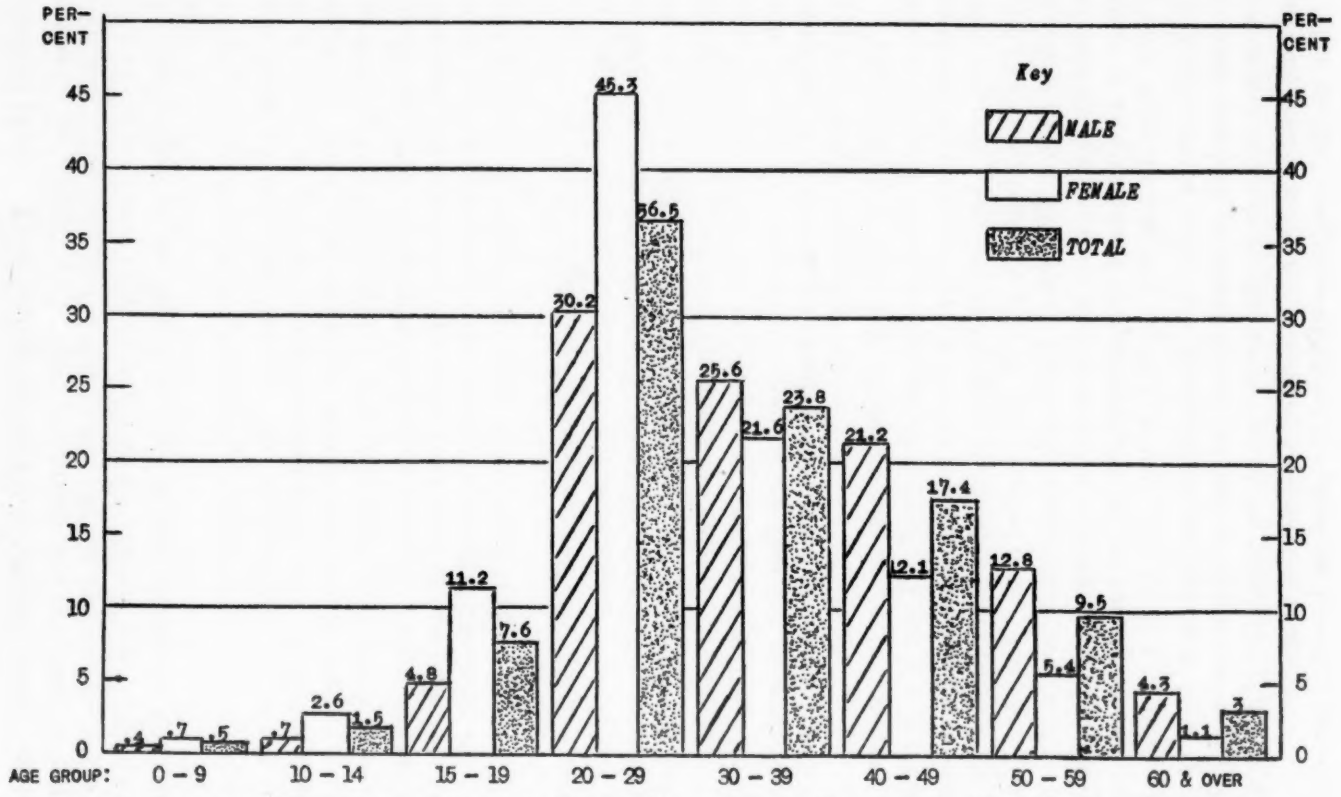

CHART 1. PERCENTAGE DISTRIBUTION ACCORDING TO AGE AND SEX OF CASES OF TUBERCULOSIS, 1930–1935, BELLEVUE-YORKVILLE CONSULTATION CLINIC

fessional group. About sixteen per cent were laborers, factory workers, students, and unemployed. The occupation of 4 per cent was not ascertained. The majority of the group (88 per cent) were adults and only 12 per cent were children under fifteen years of age. * The age and sex distribution of the diagnosed cases of tuberculosis are indicated in chart 1.

Thus this clinic has been concerned with tuberculosis in an adult white population of moderate income. The predominance of adults (over fifteen years of age) in the group would tend to give a higher yield of significant cases. The moderate income level would tend to exclude members of this group seeking either dispensary care or the services of specialists where roentgenological diagnostic facilities would be available. However, one would not expect the total yield of tuberculosis to be as great as in a poorer group or one of different racial composition, where the prevalence of the disease is usually found to be higher.

Analysis of Cases Diagnosed Tuberculous: Of the total examined (12,300) during the eight years, 10,837 were adults. Of these, 2,079, or 19.2 per cent, were diagnosed tuberculous. Of 1,463 children only 40, or 2.7 per cent, were diagnosed tuberculous. Thus of the total admissions 17.2 per cent were diagnosed tuberculous. By comparing the consultation service with the diagnostic chest clinic at Bellevue-Yorkville, Downes (1) has recently pointed out that the former was more effective in tuberculosis case-finding, 17 per cent as compared to a little less than 5 per cent during 1931.

Certain trends in the total admissions and in the percentage of admissions diagnosed tuberculous are of interest. There is a decrease in total admissions from 2,007 in 1932 to 1,593 in 1933. This corresponds with the time when similar clinics were added in other parts of the city and this clinic began to serve a more limited area. Therefore the admissions from 1933 through 1936 really represent a more intensive use of this service by the physicians of the smaller area. Despite this, there is a continuously decreasing percentage of cases diagnosed tuberculous, from 33.7 in 1929 to 16.6 in 1933, and to 13.1 in 1936. It is believed that the reason for this decreasing percentage of positive cases lies not in a lack of selectivity on the part of the referring physician, but rather in his increasing awareness of the possibility of tuberculosis and his need of assistance in making a differential diagnosis.

The cardinal symptoms which led the physician to seek a consultation

were secured by sampling 717 cases studied during 1935. A comparison of symptoms presented on admission by the three groups, diagnosed as tuberculous, other than tuberculous lesions, and no chest lesions (table 1), indicates that the referring physician wants to play safe when he elicits cardinal symptoms commonly associated with tuberculosis, and therefore feels justified in requesting the chest consultation service.

TABLE 1

Comparison of symptoms and diagnosis of 717 cases examined in Bellevue-Yorkville Chest Consultation Clinic (1935)

SYMPTOMS	NO LESIONS*	NON TUBERCULOUS LESIONS	TUBERCULOUS LESIONS
No symptoms	40	14	15
General Symptoms			
Fever	61	67	53
Fatigue	131	140	119
Chills	51	68	40
Loss of weight	110	121	106
Sweats	55	83	57
Local Symptoms			
Pain in chest	68	83	72
Cough	132	195	151
Expectoration	99	180	133
Dyspnoea	44	87	65
Haemoptysis frank	6	5	25
Haemoptysis streaking	16	31	31
Gastrointestinal	7	10	5
Laryngeal	76	100	67
Sputum positive	0	0	67
Sputum negative	159	187	97
No record of sputum	80	52	75
Number of cases analyzed	239	239	239

* Calcifications at hilum or in lung present in 26.

In this series, the general symptoms, such as fever, fatigue, or loss of weight, are found practically as often in cases which either have other than tuberculous lesions, or no chest lesions, as they are in those cases finally diagnosed as tuberculous. And again, symptoms such as cough, expectoration, and dyspnoea, which are more definitely referable to chest conditions, appear with as great or greater frequency in cases found to have other than tuberculous lesions. Therefore, if the referring physician is going to depend on symptoms alone to guide him in requests for

consultation, it follows that other conditions will be found more frequently than tuberculosis.

Recently Amberson (2) has stated that "The measure of practical effectiveness of any case-finding scheme can be expressed in terms of the percentage of *early* cases discovered."

TABLE 2

Percentage distribution according to stage of tuberculosis of 1,733 cases diagnosed during 1930–1935 in Bellevue-Yorkville Chest Consultation Clinic

STAGE		1930	1931	1932	1933	1934	1935	AVERAGE 1930-1935
I	A	16.4	9.4	14.1	17.1	16.0	10.9	13.9
	A arrested	10.3	12.6	17.9	23.2	14.3	11.7	15.0
	B	5.6	12.9	7.4	3.7	2.1	4.2	6.4
	Total—Stage I	32.3	34.9	39.4	44.1	32.4	26.8	35.3
II	A	6.9	4.8	10.6	15.9	16.0	9.2	10.2
	A arrested	1.3	1.6	2.1	2.9	4.7	2.1	2.4
	B	17.6	16.1	9.9	4.1	4.2	16.3	11.6
	Total—Stage II	25.8	22.5	22.6	22.9	24.9	27.6	24.2
III	A	0.9	3.5	12.3	16.3	16.9	8.4	9.4
	A arrested	0.0	0.3	0.4	1.2	3.0	2.9	1.2
	B	21.1	28.4	17.2	11.4	17.3	27.2	20.5
	C	19.0	9.4	8.1	3.7	4.7	5.0	8.5
	Total—Stage III	41.0	41.6	38.0	32.6	41.9	43.5	39.6
Childhood type		0.9	1.0	0.0	0.4	0.8	2.1	0.9
Total—all stages		100	100	100	100	100	100	100

In a series of 1,733 cases diagnosed as tuberculosis (1930–1935) it was found (table 2) that 35.3 per cent were diagnosed as minimal. However, 15 per cent of the total cases were classified as minimal arrested, leaving 20 per cent of the total cases diagnosed as active minimal and of no clinical significance. If only active cases are considered, for the year 1932 out of a total 273 new active cases of tuberculosis, 74 were discovered in the minimal stage, or only 26 per cent.

This is somewhat lower (chart 2) than the yield of active minimal cases found in the general tuberculosis clinics (3). Among 3,686 new

active cases admitted to and diagnosed in 1932 in the tuberculosis clinics in New York City, 29 per cent were discovered in the first stage of the disease.

Both are strikingly lower than the yield of active minimal cases found by such a routine procedure as that carried out by the Metropolitan Life Insurance Company, where since 1928 Home Office employees have been examined, fluoroscoped, and, if necessary, X-rayed at the time of

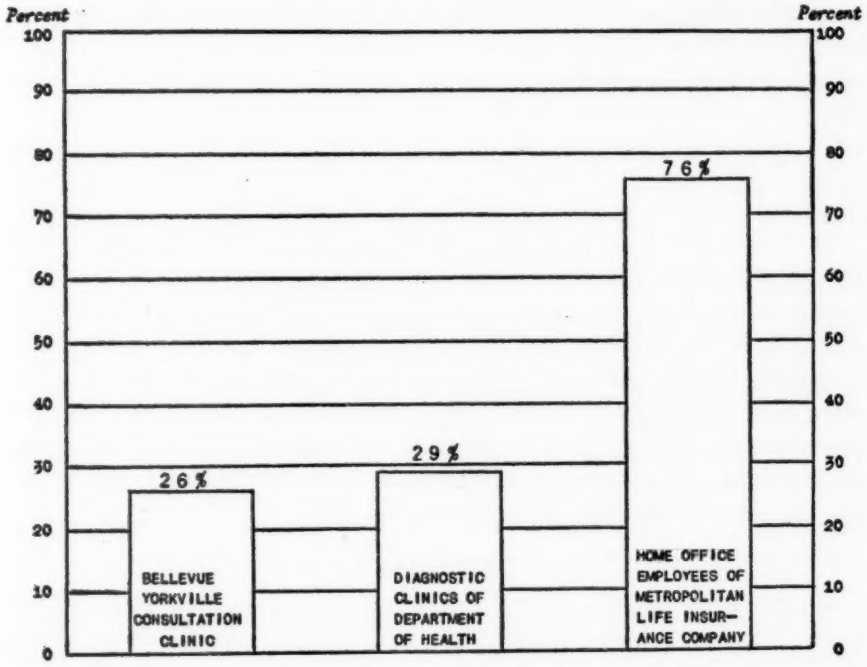

CHART 2. COMPARISON OF PER CENT OF ACTIVE CASES OF TUBERCULOSIS DIAGNOSED IN MINIMAL STAGE, 1932, IN THREE TYPES OF SERVICE

employment and annually thereafter. There, during 1932, of the 33 cases admitted to their Sanatorium, the percentages are quite reversed, with 76 per cent of the cases being minimal and 24 per cent being moderately or far advanced (4).

The diagnoses other than tuberculous lesions were as follows in a group of 239 cases, the majority of which warranted a careful examination for differential diagnosis.

Chronic bronchitis, asthmatic bronchitis, pulmonary fibrosis and emphysema	48	
Bronchiectasis, lung abscess	17	
Pleural effusion (nontuberculous) plastic pleurisy, empyema	9	
New growth of bronchus	1	
Silicosis, anthracosis	2	
		77
Acute respiratory infection, pneumonia	124	
Cardiac disease	33	
Syphilis	2	
Diabetes	2	
Lymphadenitis (nontuberculous)	1	
		162
		239

As was shown in table 1, the symptoms presented by this group did not differ significantly from those in the group finally diagnosed tuberculous, and yet the care and treatment to be instituted by the doctor would be quite different and must depend on an accurate differential diagnosis. Furthermore, 77 of the 239 cases had diseases which have often been confused with tuberculosis, with the result that such patients have frequently been sent to tuberculosis sanatoria. It is important that such cases be correctly diagnosed so that they do not improperly use the limited facilities for tuberculosis cases.

DISCUSSION

From a study of this service it would appear, first, that adequate facilities to render a good chest diagnostic service have been made available by the Department of Health; second, that a real service has been rendered to a group which, due to limited finances, might have been deprived of such help; third, that the service leads to intelligent care of patients diagnosed tuberculous; fourth, differential diagnoses on problem cases have been made, thereby rendering a service in nontuberculous diseases; and finally, the percentage of cases diagnosed in the minimal stage is considered to be low.

The discovery of such a small percentage of tuberculosis in the minimal stage is a serious defect which offers a distinct challenge. The finding of 65 per cent of the cases in the moderately and far advanced stages clearly indicates that our case-finding efforts in the main have been con-

cerned with what Kleinschmidt (5) has termed "the obvious carrier." These findings are of common knowledge to workers in the field of tuberculosis for, as has been so aptly stated by Amberson (6), "at least 60–70 per cent of tuberculous people do not develop an awareness of ill health until the disease has entered the moderately or far advanced stages." Therefore it is entirely reasonable to expect that any method which depends on the patient's having symptoms before he seeks examination will result in finding late cases.

Such lack of awareness on the part of the patient, plus his natural hesitancy at paying a doctor's fee because of what may seem to him trivial symptoms, places the private practitioner at a disadvantage as a finder of minimal cases. Furthermore, if, as Amberson's (6) experience indicates, 50 per cent of the minimal cases of tuberculosis have no abnormal signs and the remaining 50 per cent have scant signs, how can the private practitioner be expected to diagnose these cases accurately without further aid such as X-ray examination?

This necessity for some type of X-ray examination in establishing an accurate diagnosis of early tuberculosis has been repeatedly emphasized during recent years. Various routine surveys of groups of apparently healthy individuals by means of paper or celluloid films or the fluoroscope have demonstrated that in such groups an incidence of tuberculosis of from 1.2 to 5 per cent may be expected, depending on the prevalence of the disease in the particular population and age group studied (6 to 9). More significant, however, is the fact that, among cases of tuberculosis discovered in such surveys, approximately 70 per cent are in the minimal stage.

The remedy for this defect would seem to lie, not in the consultation procedure itself, but in educating the general public to go to the private physician for thorough health examinations regardless of symptoms. Since minimal tuberculosis is usually discovered only by routine X-ray study, it follows that a routine chest X-ray examination of some sort as part of the examination should be advocated for everyone. For particularly susceptible groups such as adolescents, young adults, or contacts, a semiannual examination should be urged. In such a campaign, public health agencies and tuberculosis associations can and should play an important rôle by making people health-examination as well as X-ray conscious.

It is obvious, though, that if physicians referred large numbers of patients to the chest clinics for routine X-ray studies, it would soon place

an undue burden on the available facilities. However, the fluoroscope has well established its efficiency as a practical method of case-finding (4, 7, 10) and with some experience and training in its use it might be an adequate substitute. It should be possible for the private physician to obtain experience in the use of the fluoroscope through short special courses such as are given by the various hospitals in large cities, or in special training courses offered as a project by public health agencies. In this way the private physician might act as a preliminary "screen" for reference of cases and utilize the Consultation Service for confirmation of his fluoroscopic findings by X-ray.

CONCLUSIONS

A critical analysis of the tuberculosis case-finding results at a chest consultation service has demonstrated that, while the efforts are fruitful, it mainly brings to light late-stage tuberculosis. This is felt to be inevitable if physicians refer cases mainly because of symptoms or physical signs. In order to find more minimal tuberculosis, extension of X-ray facilities, particularly fluoroscopy, as part of the routine periodic health examination is advocated.

The authors wish to acknowledge the assistance of Mr. Harry Goode in the statistical analysis. Messrs. Samuel Stone, Martin Gerson and Benjamin Lewis, members of the fourth year class (1937) at New York University, College of Medicine, assisted in studying the clinical records.

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THE PUBLIC HEALTH ASPECT OF THE TUBERCULOSIS SANATORIUM[1]

CHESLEY BUSH[2]

To-day we have come to accept as an axiom the following statement: "Prevention and treatment in tuberculosis go hand in hand, and one cannot be divorced from the other without detriment to both." With this in mind—that every case is to be considered as a problem of public health as well as of treatment—we may well ask ourselves several questions. Are sanatoria and institutions for the tuberculous operated with this point in view? Can they be fitted into modern public health programs in tuberculosis? How can each one of us fit his own sanatorium into such a program?

We bring your attention to this problem with some hesitation. We realize that many communities have met and are meeting this problem in a most intensive and extensive manner. We realize that there is no perfect solution. Governmental and nonofficial health agencies vary so much in organization in different localities that no one plan can fit all situations. But we believe that certain fundamental principles are constant in all communities, and that they can be applied with benefit to the individual patient and to tuberculosis prevention programs everywhere.

The name "sanatorium" or "sanitarium," representing institutions for the care of the tuberculous, has been linked with the disease since the time of Brehmer and Detweiler. Institutional care has antedated the discovery of the tubercle bacillus. It has been the ideal method of treating individual cases of tuberculosis. This was particularly true during the period when modified rest and dietetic hygienic programs were all that could be offered to tuberculosis cases. Admission to an institution then dated the beginning of treatment and patients were retained until the disease was apparently arrested, the efficiency of the sanato-

[1] Presented at a Joint Symposium of the Pathological, Clinical, Social Work and Administrative Sections at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 3, 1937.

[2] Arroyo Sanatorium, Livermore, California.

rium being measured by the length of stay of the patient and the infrequency of readmissions. Particularly was this the ideal striven to be attained by well conducted private sanatoria. They led the way and no doubt contributed a great deal to the tremendous growth in institutional beds in the United States during our generation. These institutions have been great factors in the public health aspect of tuberculosis through isolation and education. But, in some parts of the United States, particularly in our state of California, we have approached the control of tuberculosis as a communicable disease through the "building" angle, the "brick and mortar" route; and we are now faced with the situation that there is a great deal to do in the control of tuberculosis that has no connection whatever with buildings, that tuberculosis appears more and more to us, as does any communicable disease, the responsibility of a health department. And we find that health departments and other public welfare agencies have no connection with many of our sanatoria; in fact, many sanatoria are conducted in direct opposition to them. We find that many sanatoria cannot possibly give the necessary isolation and the necessary education to the groups of tuberculous patients needing them because of the continued long stay of patients who might well be cared for under other conditions.

Our present situation with approach to the public health control of tuberculosis by way of the instituion is in direct opposition to that of the English plan. It might be well for us to study the English situation where every county heads up in a tuberculosis official who has control of the whole aspect of tuberculosis—prevention, treatment and welfare.

Our present dilemma in regard to "buildings" rather than functional organization may be explained psychologically. It is easy to sell to the public the value of something that they can visualize, such as a building. It is hard for them to visualize a nebulous program of clinics and doctors' offices and public health officers and social workers. Illustrating this is the recent incident of the Wisconsin Anti-tuberculosis Association when it recommended to the trustees of the Willard bequest a modern tuberculosis program in regard to children and obtained instead some buildings. As long ago as 1927 I failed to prevent the addition of a building to our so called preventorium unit in Alameda County for the same reason. This psychological need of human beings for visual demonstration and education makes it necessary for us to send patients to sanatoria in order that they may learn the proper method of conducting their lives and the proper adjustments in regard to their disease. The

point of view there obtained in a relatively short period of time cannot be equaled by any other method of teaching by the average physician.

In Alameda County we have a sanatorium upon a hill, a sanatorium with which I am associated. The average person in Alameda County tends to visualize that sanatorium as the whole tuberculosis program, from beginning to end. The average question is: "Doctor, how many patients does Arroyo cure of tuberculosis?" The psychology of the situation is such that even our patients feel that admission and discharge spell diagnosis and arrest, and in our educational program we try carefully to counteract these tendencies. The real teaching of visualization of tuberculosis as a communicable disease and, as Doctor Parran has said, an eradicable disease, will have to come in these instances through the sanatorium men themselves, who will have to rise above petty differences and assume leadership. These men will find that correlated care of tuberculosis will raise the efficiency of institutions in caring for tuberculosis as a disease and, while not interfering with the care of the individual patient, will far increase the educational and isolation value of the institution to the community.

The following is the story of one public institution (Arroyo Sanatorium, Alameda County, California) in an attempt to operate with a maximum public health efficiency. This institution was opened twenty years ago and has passed through the various phases of our epidemiological outlook on tuberculosis in that time, and has been operated according to the best ideals of the moment, first, as an institution housing all types of tuberculosis, second, as an institution housing only minimal and moderately advanced tuberculosis and applying a length of stay averaging thirteen months with the usual modified rest programs and with a small amount of collapse therapy. Far advanced and chronic far advanced tuberculosis was housed elsewhere, but poor prognosis and advanced disease were criteria for discharge or nonadmission.

During these two periods of operation the institution had no direct connection whatever with any clinic, welfare or tuberculosis society, and had no control of patients before or after admission. A waiting list was always present. Over fifty per cent of the patients received ambulant care and patients were not discharged until accustomed to full working efficiency within the institution. The sanatorium was ideal for the individual patient who could obtain admission.

By gradual infiltration of the sanatorium into out-patient care, and by a change in county organization it became possible in 1933 to coördinate

the tuberculosis activities of all out-patient clinics, medical society, tuberculosis society, and public hospitals with the santorium, forming an organization headed by the sanatorium administrator, but having the defect of a very weak and loose contact with the nine health departments of the county. The function of the health department, which should assume the leadership, is made impossible by the disorganization of our county in this regard. All tuberculosis patients in the county are divided into two groups, indigent (70 per cent) and nonindigent (30 per cent). The county assumes the care and management of the indigent group, and the tuberculosis association, together with the medical society, assumes the care and management of the nonindigent group. In this latter group the private sanatorium assumes its responsibility.

The public sanatorium (Arroyo) has been coördinated to the public health program in the following ways:

1: All adult patients with tuberculosis and with active disease and positive sputum are admitted to institutional care for (a) community isolation and (b) tuberculosis education.

2: The public health aspect is emphasized immediately upon admission. The medical staff brings pressure to bear upon the patient to see that all his or her contacts are examined immediately, if not already done by physicians in the clinic or privately. Each physician also begins to plan social rehabilitation of the patient at the same time that medical treatment is being carried on. The patient is regarded as one unit of a family or community problem, as well as an individual.

3: Collapse therapy is used when possible (75 per cent of sanatorium population), (a) as a public health method and (b) as a treatment method.

4: The patient is discharged as soon as his disease comes under control, and when his sputum ceases or is negative on microscopical examination. (Stomach washings are probably not an extremely important epidemiological consideration.) There is usually a minimum of three months here applied. On the other hand, collapse therapy is maintained for a minimum of at least three years from date of adequate collapse (negative sputum). This work is carried out in clinics under the coördinated direction of the sanatorium, or by private physicians on a part-pay plan. Patients are readmitted at will for necessary periods when any complication arises requiring institutional care. Readmissions no longer constitute criteria of recrudescence of disease in arrested cases.

5: Advanced chronic cases are submitted to surgery when possible. Continuous positive sputum and difficult home problems are sufficient cause for retention in the sanatorium indefinitely. The terms minimal, moderately advanced,

and advanced tuberculosis are no longer criteria for admission to the sanatorium.

6: Where patients are not suitable for rehabilitation on the outside, the sanatorium is operated in part as a colony using as its working staff, where possible, chronic patients.

7: The sanatorium becomes a teaching institution for physicians, nurses and social workers who are caring for tuberculosis in the county-wide program, and consultation is freely given to members of the medical society when requested.

The results of operation under a public health viewpoint are as follows:

1: There is no waiting list in county institutions for tuberculosis (Arroyo and Fairmont), save for a few weeks in the spring of the year. Vacant beds are common, and chronic nontuberculous pulmonary infections are housed in quarters formerly used for tuberculosis patients. Minimal lesions can be cared for immediately.

2: A large portion of the treatment load of patients having had sanatorium education and experience is carried on in the clinics, together with contact examination and reëxamination of quiescent cases. Relief funds are available for food and housing if necessary. The number of clinic visits in 1936 was over 10,000, as compared with 3,000 clinic visits in 1933. The tuberculosis society has created scholarships for young physicians practicing in the county to work in the lung clinics.

3: Turnover of the institutions (Arroyo and Fairmont) has been materially increased, in fact, almost doubled despite the fact that many patients are, for certain specific reasons, carried on a full sanatorium program of thirteen months or, if necessary, for an indefinite stay.

4: The number of physicians in Alameda County interested in and working with tuberculosis and not directly employed by county institutions has increased from two to sixteen, while the medical society is coöperating in examination and diagnosis of part-pay (nonindigent cases) to the extent of approximately 500 examinations in 1936. This latter work is done through the coöperation of the Alameda County Tuberculosis Association.

5: The number of minimal cases in residence at the end of 1936 had risen to 20 per cent of the total, and the length of time between beginning of clinical disease and diagnosis of tuberculosis, in two comparable groups of fifty patients, has fallen from six months to two years (1933) to from one to six months (1936).

CONCLUSIONS

1. The point of view of public health in operating a sanatorium has been described in detail for one institution.

2. The old criterion of minimal, moderately advance, and advanced tuberculosis no longer appertains to admission or discharge of patients from sanatoria operated with this point of view; and readmissions may be as many as necessary. They do not measure efficiency of sanatorium care as they did under the old regime.

3. Patients are discharged when considered safe residents of their own homes, and readmitted whenever such safety disappears. Treatment and supervision is continuous.

4. We find that operation of sanatoria with a public health point of view results in an increase of bed capacity, not by the addition of more beds, but by a more efficient use of beds already available.

PRACTICE IN TUBERCULOSIS CLINICS IN THE UNITED STATES

An Analysis of Data Obtained by Questionnaire in a Survey of Tuberculosis Clinics[1]

MARION NELSON[2]

INTRODUCTION

In connection with the question of preparing suitable standards for the maintenance of tuberculosis clinics, there was appointed during the summer of 1934 by the President of the National Tuberculosis Association a Committee on Clinic Standards. The following members have served on this Committee from its beginning:

Dr. Herbert R. Edwards, Chairman
Dr. Vera V. Norton
Dr. Marvin F. Haygood
Dr. H. I. Spector
Mr. Arthur M. Dewees, Secretary

At an early meeting of the Committee it was arranged to inaugurate a survey of existing clinic facilities in order that the Committee might have more accurate knowledge of current clinic practice throughout the United States. It was felt that the Committee would thereby be in a better position to evaluate existing practices that might be incorporated in clinic standards for communities in need of such service. Accordingly, work was begun on the preparation of a questionnaire for securing pertinent information from the various clinics.

Preliminary to making such a survey of clinic facilities it was necessary to make an up-to-date census of the existing tuberculosis clinics throughout the country. Such a census had not been made since early in 1929 when the National Tuberculosis Association sought to determine simply the number of clinics in existence at that time. In addition to its being several years old, the information obtained in that census was not suffi-

[1] Prepared for the Committee on Clinic Standards of the National Tuberculosis Association.
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ciently complete to permit its use in this instance. Accordingly, the first step toward the contemplated survey of clinic facilities and practices was the making of a new census of the clinics which would furnish the detailed information called for on the schedule which was being prepared.

PRELIMINARY CENSUS

In order to obtain this list of tuberculosis clinics in the United States, the Committee on Clinic Standards sought the assistance of state tuberculosis associations throughout the country early in 1935. Many of the state associations, in turn, enlisted the aid of their affiliated local groups and other agencies in making a census of existing clinics in their respective states. All states responded but one small state in which it is safe to assume that no great amount of clinic service exists. It seems probable, therefore, that a reasonably complete census was obtained by this method.

After editing these census returns by eliminating duplicates and reports of school clinics, there remained approximately 1,000 clinics of a permanent nature. There were four states in which there were no permanent clinics and where the only clinic service is of an occasional character at irregular intervals. For four other states there was only a single permanent clinic reported, supplemented by a traveling unit in two states. In the remaining states, the number ranged from two or three up to more than 100 in the two largest states, New York and Pennsylvania.

Approximately half of the states reported clinic service rendered by a traveling unit or by occasional clinics, or both, in addition to the existing permanent clinics. About half of the traveling units were operated by state agencies and the other half by local agencies. In a few cases the service rendered by these traveling or itinerant units was of a permanent nature, that is clinic sessions were held at regular intervals, in some instances as often as once a week, at established, permanent centres. In most instances, however, the service rendered by such units was irregular in nature, with sessions at less frequent and less regular intervals.

COLLECTION AND ANALYSIS OF QUESTIONNAIRE DATA

A schedule calling for information on forty-four items was mailed to the designated representative of each clinic, as furnished on the census

blanks which had been received. The statistical data requested pertained to the year 1934, and the completed schedules were prepared for tabulation with that year as the basis for the resulting compilations. A few of the completed schedules were excluded from the analysis as a result of editing on this point, such as those established since 1934 and those reporting a lapse in activity during 1934. Certain others, relatively few in number, were also excluded because it was felt that the reported set-up failed to come within the purview of the present study of clinics and clinic practice. Principal among these were sanatoria which reported a very definite service but no regular clinic sessions, their consultation and diagnostic service being rendered by appointment, upon request, or as the opportunity presented itself for the examination of relatives or other visitors to patients.

Types of clinics and agencies conducting them: After the exclusion of such schedules, there remained a total of 639 to form the basis of the tabulations which were made. All but 67 were classified as permanent clinics, permanent having been defined as operating on a scheduled time and place basis. Thirty of the 67 were classified as itinerant, this term being applied to those set-ups having a continuing program but operating on an itinerant basis. The other 37 were classed as occasional or non-permanent clinics, those without a continuing policy or program.

Although some clinics were sponsored by two or more agencies, all were classified on the basis of the one regarded as the principal sponsoring agency. Slightly more than one-third of all the clinics were conducted by official health departments, state and local. The next largest number, 177 in all, were conducted by state or local tuberculosis associations, and third in importance as a sponsoring agency was the tuberculosis sanatorium with 105 clinics. The remaining clinics, 137 in all, were conducted by hospitals other than tuberculosis hospitals, both public and private, and by various other agencies, both public and private, such as official tuberculosis control groups operating independently of the health department, various nursing groups, medical schools, etc.

Date of establishment of clinics: Of those clinics (slightly more than three-fourths of all) for which the date of establishment was reported, more than two-thirds were established during the fifteen years since 1920. The five year period from 1920 through 1924 was the period of greatest development, more clinics having been established during these years

than during any other similar period of time. Permanent clinics conducted by tuberculosis associations and by tuberculosis sanatoria particularly have been a development of the more recent years (since 1920), those sponsored by health departments, other hospitals, and other public and private agencies dating their establishment to the years before 1920 in just about as many instances as to the years since 1920. Itinerant clinic services, to a greater extent even than those of the permanent type, have been a development of the more recent years, all but seven of the 26 for which this information was given having been established since 1920 and only two previous to 1915.

Major activity of clinics: Under this item the schedule called for information as to which of the three activities, consultation, diagnosis or treatment, might be considered the major activity of the clinic. Seventy per cent of the entire number indicated consultation or diagnosis, or consultation and diagnosis as of major importance, with only a very small number, 18 in all, designating consultation alone as the major activity. Whether or not all of these may be considered consultation clinics in the same sense is perhaps questionable, since the word has come to be used as descriptive of a very special type of service, whereas it is felt that in most instances it has been used in its more common, every-day meaning. The remaining 30 per cent of all clinics mentioned, as their major activity, treatment or follow-up in conjunction with consultation or diagnosis or both; and only five clinics were devoted mainly to treatment, and four of these five were strictly pneumothorax stations. Those clinics classified as itinerant were almost wholly for consultation and/or diagnosis, only four of the 30 mentioning treatment or follow-up in addition. All of the occasional clinics, as would be expected, were wholly for consultation and/or diagnosis.

Items for which charges are made: Two-thirds of all the clinics reported no charges for their service. Among the remaining one-third, indicating charges made for one or more items, such as admission, X-ray films, medicines, and laboratory examinations, X-ray films constituted the principal item for which the patient was requested to pay. In almost every instance, however, it was stated that a very nominal price was asked, generally only a part of the actual cost, and that only of patients who could afford to pay. Only thirty-four clinics, including one of the occasional type, reported an admission fee, most of them indicating a

small charge for other items as well. In practically every case where a charge for any part of the service was made, either the amount charged or the payment of any amount was contingent upon the patient's ability to pay.

Economic considerations in admission to clinics: Well over fifty per cent of all clinics stated that admission was not determined by the economic status of the patient. The remaining 43 per cent reported that economic considerations did determine the patient's eligibility, 38 of them (6 per cent of the total) stating that this applied only to subsequent visits and not to the first admission. For the most part, this eligibility was determined by personnel attached to the clinic or to the agency conducting the clinic, such as social service workers, nurses, supervisors, etc. Forty-four, or 16 per cent of all clinics admitting patients on the basis of economic status, indicated that the physician, nurse, or agency referring the case determined the patient's eligibility.

Necessity for referral by a physician: Only ninety-nine, or 15 per cent of all clinics, reported that patients were required to be referred by a physician. Of the various agencies conducting clinics, tuberculosis sanatoria require such referral to a greater extent than any other agency, with 38 per cent of the permanent clinics under their sponsorship indicating such a requirement. Also, a greater proportion of the itinerant and occasional clinics than those of the permanent type require referral by a physician, and although the numbers involved in these two types of clinics are small it seems logical that such should be the case in view of their nature.

Use of clinics as teaching centres: Although as many as 253, or 40 per cent of all the clinics, reported and were classified as having one or more groups for whom the clinic was used as a teaching centre, only 93 reported any definite affiliation with a medical school, a hospital, a nurses' training school, or some other similar agency. The group mentioned most often was physicians, mostly the "occasional physician." Medical students or internes constituted the next largest group, 56 clinics in all reporting one or the other, particularly medical students. Twenty clinics reported two or more groups, such as physicians and nurses or medical students and nurses, and 5 clinics reported nurses, graduate or student. It is difficult to determine in just how many instances the teaching was formal

in nature, but it is probably fair to assume that the number would not exceed the 93 which reported an affiliation with a medical school, a hospital, or nurses' training school. The affiliation most frequently reported was with hospitals, 48 clinics indicating such an affiliation, all but four of them hospitals other than those for the treatment of tuberculosis. Medical schools were indicated as the affiliate by 37 clinics, and various other health or medical agencies by 8 others.

Availability of X-ray, fluoroscope, and laboratory facilities: Of these three aids to diagnosis, laboratory facilities are the closest to being universally available to all clinics; all but 8 clinics, one permanent and seven occasional, indicating access to such facilities, and even in the case of these 8 it seems probable that the question may have been incorrectly answered. All except 140 clinics, 22 per cent of the total, specified that these laboratory facilities were outside of the clinic, mainly in state and local health departments.

X-ray apparatus was reported available by all but 4 per cent of the clinics, a larger proportion of the occasional clinics reporting negatively in this regard than either of the other two types. Less than one-third of all clinics indicated that such apparatus was available in the clinic proper, although an appreciable number of the others, especially those conducted by hospitals and those using hospital space, stated that it was available in some other part of the hospital or other very nearby location. Only 2 of the occasional clinics and as many as 11 of the itinerant group indicated that X-ray apparatus was available in the clinics.

A considerably greater proportion of clinics, 16 per cent, reported that no fluoroscope was available. Compared with X-ray apparatus, a somewhat smaller proportion, 25 per cent of all clinics, reported a fluoroscope in the clinic proper, although as in the case of X-ray apparatus an appreciable number of the others had such equipment available at some nearby location. Only 2 of the occasional clinics and 3 of the itinerant clinics reported a fluoroscope as part of the clinic equipment.

Use of tuberculin and lipiodol: More than 90 per cent of all clinics reported the use of tuberculin, most of them the routine use of it, as a diagnostic aid in children. More than two-thirds of them reported either its routine use or its occasional use in adults. Slightly more than one-fourth indicated the use of lipiodol, either routinely or occasionally. More than 50 per cent of the clinics indicating its use were those con-

ducted by tuberculosis sanatoria and other hospitals, whereas they constituted only 23 per cent of all clinics covered in the study.

Methods used in examining sputum: The direct smear was the method most frequently reported as the usual method employed in studying sputum, 45 per cent of all clinics which were able to give this information having indicated this method. An additional 18 per cent stated that both the direct smear and either concentration or culture methods were regularly used, and 25 per cent more reported the regular use of all three methods, a considerable number of them adding that animal inoculation was also employed upon occasion. The remaining 12 per cent reported either concentration or culture or a combination of these methods as the ones generally used. Only one occasional clinic reported that no tests were made, but it is possible that there were others making no tests among those clinics which furnished no information on this point and which were thrown in the unspecified group.

Usual number of physicians at each clinic session: Information on this point was subdivided into white and Negro medical personnel. All but 8 of the clinics reported one or more white physicians in attendance at each clinic session. More than two-thirds of all clinics reported a single physician in attendance; an additional 17 per cent, 2 physicians, and 8 per cent more, 3 physicians at each clinic session. A small proportion, about 5 per cent, reported 4 or more at each session. Altogether, 29 clinics reported one or more Negro physicians in attendance along with white physicians except in the 8 instances mentioned above. For all but 4 of these clinics which reported 2 or more Negro physicians there was only a single Negro physician in attendance.

Usual number of nurses at each clinic session: Information on this point was likewise subdivided into white and Negro personnel. In 10 clinics there was either no white nurse in attendance or no nurse at all. Considerably fewer of the clinics reported a single nurse in attendance at each clinic session than was the case with medical personnel. Two nurses were more frequently reported, 42 per cent of all clinics indicating this as the usual number, compared with 37 per cent reporting one nurse. Eighteen per cent reported three or more nurses at each clinic session. Fifty-seven clinics reported Negro nursing personnel in attendance at the sessions, about double the number reporting Negro medical person-

nel. Forty-two of them indicated one Negro nurse and 15 indicated two or more.

An especially large proportion of the occasional clinics reported more than one or two physicians and nurses in attendance at each clinic session. The reason for this doubtless lies in the very nature of such clinics and the methods used in organizing them. It is probably safe to say that all do not take part in the actual conduct of the clinic in the same sense that would apply to clinics of the permanent type with a large medical and nursing personnel.

Other clinic personnel: Under this item information was obtained concerning the number of clerks, stenographers, technicians, etc., attached to the clinics. Less than half of all the clinics reported other personnel, the remainder either specifying that there was none or leaving this item unanswered which probably in most cases should be interpreted as meaning that there was no other personnel attached to the clinic. Of those reporting other personnel, more than 60 per cent indicated only one other worker and an additional 24 per cent indicated two, leaving 15 per cent with as many as three or more in addition to medical and nursing personnel. A few reported volunteer clerical helpers, especially the smaller clinics and those of the occasional type. A larger proportion of the clinics conducted by hospitals and by official tuberculosis control groups operating independently of health departments reported additional clinic personnel, than did those conducted by health departments, tuberculosis associations, and other unofficial agencies.

Payment of medical staff: Under this item information was asked concerning the usual hourly rate of payment in 1934. Relatively few, only slightly more than one-fourth of all clinics, were able to report on this basis. A somewhat smaller number reported amounts paid on some other basis, making in all slightly more than 50 per cent of the clinics which reported definite amounts paid the medical staff. The remaining clinics, close to 50 per cent, reported that the medical staff was not paid, but an unduly large proportion of these were in the group conducted by tuberculosis sanatoria and other hospitals. In most instances the reports from such agencies stated that the regular staff was used in conducting the clinics and that the members were not paid specifically for their clinic work. In just how many clinics the medical staff actually served entirely without remuneration it is difficult to determine, but it seems safe to say that the number would be comparatively small.

Of the 175 clinics reporting a definite hourly rate, the amount most frequently reported ranged between $2.00 and $2.50, 49 of them falling in this group. Forty-four of these clinics were among those conducted by state or local health departments. The amount reported second in order of frequency was $5.00 or more, with 37 clinics coming within this classification, 15 of these clinics conducted by local tuberculosis associations. Third in number were those clinics reporting an hourly rate ranging between $3.00 and $3.50, 35 clinics in all, of which 33 were among those conducted by local health departments. These three groups constituted 69 per cent of the clinics which reported an hourly rate, the remaining clinics being distributed as follows: less than $2.00, 29 clinics; from $2.50 up to $3.00, 18 clinics; from $3.50 to $5.00, 7 clinics. An average rate, figured on the basis of the reports from these 175 clinics, would fall somewhere around $3.00.

Salaries of nursing staff: Information on this point was expressed on an annual basis with slightly more than half of all clinics reporting. The salary most frequently reported by these 324 clinics ranged between $1,500 and $1,800 annually, 46 per cent of them falling in this classification. A relatively small proportion, 15 per cent, reported annual salaries above $1,800 and the remaining 39 per cent fell in the group below $1,500, the majority of them between $1,200 and $1,500.

Administration and reading of tuberculin tests by clinic nurses: Among the 599 clinics reporting the use of tuberculin and the practice of the clinic in this connection, the greatest number, 44 per cent, stated that the clinic nurses read the tuberculin tests but did not administer the tuberculin. An almost equal number, amounting to 41 per cent of the total, reported that the nurses neither administered nor read tuberculin tests. Thirteen per cent reported that it was the practice for the nurses to both administer and read tuberculin tests, and the few remaining clinics, about 2 per cent, indicated that the nurses administered the tuberculin but did not read the reactions.

Assignment of clinic nursing program to other nursing organizations: Fifty-eight per cent of the clinics furnishing information on this item reported that none of the clinic nursing program was assigned to other organizations. A few reported no nursing follow-up or follow-up by other than nursing personnel, namely social service workers attached to

the clinic or to the agency conducting the clinic. Of those clinics reporting assignment of any of the nursing program to other nursing groups, 41 per cent indicated that there existed an arrangement whereby both the nurses attached to the clinic and those of one or more other agencies carried on a joint program. Almost as many, 36 per cent, reported the assignment of the nursing program to the personnel of an official agency; 17 per cent to the personnel of a nonofficial agency; and the remaining few to the personnel of both official and nonofficial agencies.

Extent to which pneumothorax treatments are given: Slightly more than one-fourth of all the clinics reported that pneumothorax treatments were being given. Of those clinics making such a report, about two-thirds indicated that both initial treatments and refills were being given and one third indicated refills only. Forty-five per cent of all clinics rendering such service were among those conducted by tuberculosis and other hospitals whereas they constituted but 23 per cent of all clinics in the study. That the practice is becoming more and more widespread is evidenced by the fact that a number of clinics reported plans to make such service available, including a single system of 29 clinics in all of which pneumothorax treatments had recently been started.

Extent to which other forms of collapse therapy are used: A small proportion, 7 per cent, of all clinics reported the use of other forms of collapse therapy, principally phrenic nerve surgery. Other forms of collapse therapy indicated were pneumonolysis, scaleniotomy, thoracoplasty, and oleothorax. As in the case of pneumothorax treatments, an unduly large proportion of the clinics reporting the use of such surgical methods were among those conducted by tuberculosis and other hospitals, 70 per cent of them falling in these classifications. There is some doubt as to whether or not the reports on the use of such procedures can be literally accepted as strictly clinic procedures, especially since such a large proportion of the clinics were those conducted by hospitals. It seems more probable that the use of such surgical methods would be by special arrangement in the case of certain clinic patients rather than an actual clinic procedure.

Use of heliotherapy: About two-thirds of all clinics reported that heliotherapy was not in use. Of the 206 clinics which did report the use of heliotherapy, all but 22 per cent indicated its use outside of the clinic.

Well over half of the relatively small number indicating its use in the clinic were among those clinics conducted by sanatoria or other hospitals.

Supervision of clinic cases in the home: Relatively few of the clinics, less than 10 per cent, reported no supervision of clinic cases in the home. Of those clinics furnishing information on home supervision, about 56 per cent reported that the clinic personnel was responsible for such supervision, consisting largely of nursing supervision. An additional 25 per cent indicated that the clinic personnel along with the family physician or one or more nursing agencies were jointly engaged in the home supervision of clinic cases. A few reported that the patients were referred back to the family physician and the others that the personnel of local official or nonofficial agencies, or both, acted in a supervisory capacity in the home. The supervision of clinic cases in the home was more frequently assigned to other agencies in the case of both the itinerant and the occasional clinics than in the case of the permanent clinics. This was also true of the clinics conducted by sanatoria and other hospitals.

Experimental and research work in clinics: Sixty-four clinics reported some experimental or research work being carried on. Eight of them reported work with BCG and another agency with nine clinic stations reported a special BCG laboratory. Four clinics reported experimentation with gold therapy, and a similar number indicated tuberculin testing or X-ray studies in progress. Thirty-five were classified as carrying on two or more kinds of experimental or research work, 29 of them making up one system of clinics in which it was reported that studies were being made of the effect of contact on the Mantoux reaction, the effect of pneumothorax treatment on the Mantoux reaction, and a lipase diet in treatment. Another system of 4 clinics in this group of 35 indicated experimental work with gold therapy, sanocrysin, lipiodol, and tuberculin. The other two reported studies of collapse therapy results, BCG, tuberculin standardization, and epidemiological studies. Several other clinics stated that experimental work was being carried on but failed to specify the nature of it, and a few others indicated other research work such as studies of the reliability of tuberculin reactions and initial pneumothorax inductions in the clinic. Practically all of the experimental and research work was reported by clinics located in large cities.

Total number of clinic sessions in 1934: Only 2 of the clinics failed to report the number of clinic sessions held in 1934, making a grand total of 59,671 sessions reported by 637 clinics——55,724 sessions by 570 permanent clinics, 3,894 by 30 itinerant clinics, and 53 sessions by 37 occasional clinics. Based on these totals, the permanent clinics held annually an average of 98 sessions; the itinerant clinics, 130 sessions; and the occasional clinics, one and one-half sessions.

Night sessions for diagnosis were reported by 83 of the permanent clinics and one of the itinerant group, 3,905 sessions and 50 sessions, respectively. Night sessions for pneumothorax treatments were reported by 18 of the permanent group and one of the itinerant group of clinics, 1,445 sessions by the former and 27 by the latter. No night sessions were reported by the occasional clinics.

Number of sputum tests and X-ray films in 1934: Four hundred and nineteen, or 66 per cent of all the clinics covered in this study, furnished data on the number of sputum tests made in 1934. The remaining third either made no tests or they were unable to furnish figures on this point. A total of 220,066 tests were reported by the 419 clinics furnishing figures, 196,747 tests by 393 permanent clinics, 22,978 by 13 itinerant clinics, and 341 tests by 13 occasional clinics.

A somewhat larger number of clinics furnished figures on the number of X-ray films taken in 1934, 490 clinics reporting a total of 238,412 films. The remaining 149 clinics either took no X-ray films or were unable to furnish the data.

Number of pneumothorax treatments given: Sixty of the permanent clinics reported a total of 1,404 initial pneumothorax inductions. One hundred and four permanent clinics and two of the itinerant clinics reported 73,060 and 574 refills, respectively, both of the itinerant clinics being among those conducted by tuberculosis sanatoria.

Home visits and visits to the clinic in 1934: Approximately two-thirds of all clinics furnished data regarding the number of home visits to clinic patients during 1934, a total of 1,142,214 home visits being reported by 417 clinics. The remaining 222 clinics were either unable to supply the figures on this point or else were in that group of clinics which reported no supervision of cases in the home.

Five hundred and seventy-eight clinics, all but 10 per cent of the total,

furnished figures on the number of visits made to the clinic during 1934. These visits totalled 1,229,320.

Criteria for discharge of clinic patients: Under this item no attempt was made to classify the more obvious reasons for discharge which were mentioned on a great many of the schedules, such as death, removal to other communities, inability to locate, etc. Since replies of this sort represented the only answer to this question on a considerable number of the schedules, only slightly more than two-thirds of the schedules were actually classified under this item, and not all of these relate to the tuberculous condition of the patient. Almost half of this number, or 199 out of 433 clinics, stated only that the nontuberculous were discharged or that patients were not treated or followed, the clinic being for diagnostic purposes only. The remaining 234 clinics, therefore, comprised the group which supplied information pertaining to the discharge of tuberculous patients. Seventy-eight of these gave "negative signs of activity" and 77 gave "arrested" or "healed" as their criteria for discharge. Sixty-one others stated that they did not discharge their tuberculous patients, explaining that patients were followed for an indefinite period, with less frequent check-ups after an arrest of the disease. Another group of 17 clinics, all sponsored by the same agency, stated that patients were discharged "when restored to full working capacity on recommendation of physician."

Distribution of printed instructions and other educational matter: Only 53 clinics, or 8 per cent of the total number, responded negatively to this question. Half of these clinics were among those conducted by tuberculosis sanatoria and their reason for not doing so doubtless lies in the nature of the principal service which many of them render, namely, that of follow-up of former sanatorium patients. It is also probable that in some cases the agency doing the follow-up was responsible for the distribution of literature, although this was not definitely indicated.

Other educational efforts: Two-thirds of all clinics made some response to this question. The remaining third either failed to indicate any further educational efforts or definitely stated that no other educational work was carried on. The most frequent response to this question was instructive home visits, but such educational work is more of a routine measure common to practically all clinics and can scarcely be regarded

as a special effort at education belonging to only a limited number of clinics. Next in order of frequency was the statement that a general health education campaign, or the enumeration of educational measures constituting a general health education campaign, was being carried on. A large proportion of the clinics making this response were among those conducted by tuberculosis associations. It would seem that such educational work more properly represents the program of the sponsoring agency itself rather than the clinic, although it is doubtless true that in some instances the program of general education definitely revolves around the clinic and its activities. In any event, it is probably difficult in many cases to make a definite distinction in this regard. Other clinics mentioned talks and lectures before various groups, school surveys and children's camps, radio talks, newspaper articles, the use of posters, films and follow-up letters as educational measures.

Expenditures during 1934 and sources of funds: Only 228 clinics, or slightly more than a third of the total group, were able to furnish information concerning expenditures during 1934. This number reported total expenditures of almost $1,300,000.

Exactly half of the 604 clinics which furnished information as to their sources of funds were supported entirely by public funds, either state or local, or both. An additional 21 per cent were supported in part by public funds, various combinations of public and other funds being reported, such as Christmas Seal funds, Community Chest funds, and other voluntary or private funds. Another 20 per cent were classified as entirely supported by Christmas Seal funds, and the remaining 9 per cent by Community Chest, other voluntary or private funds, or by funds obtained from two or more nonofficial groups. Practically all of the occasional clinics and almost half of the itinerant group were supported wholly or in part by Christmas Seal funds, compared with 39 per cent of the permanent clinics.

GENERAL REVIEW AND SUMMARY

The Permanent Clinic

The foregoing analysis of clinics and their practices yields the following composite picture of the "typical" permanent clinic.

Housed in any one of a variety of places—a special dispensary building,

a sanatorium or some other hospital, a public building such as a city hall or a health department building, or in some other community building—the "typical" clinic is almost certain to have been established at some time subsequent to 1900 and probably at some time in the fifteen years since 1920. The chances are about equal that the clinic is conducted by one of a variety of official agencies or by one of a variety of nonofficial agencies. Its principal purpose is the diagnosis of tuberculosis, without charge to the patient for the service rendered. In all probability the patient's eligibility to attend the clinic is not contingent upon his economic status nor will it be necessary for him to be referred for examination by a physician.

X-ray apparatus is undoubtedly conveniently available but in all probability it is located somewhere outside the clinic proper. Fluoroscopic equipment is likewise available, somewhat less frequently than X-ray and probably outside of the clinic proper. The laboratory facilities of a state or local health department probably furnish the laboratory service required by the clinic and the smear method of examining sputum is probably used routinely. Tuberculin is used as a diagnostic aid in the examination of both children and adults, but it is unlikely that lipiodol is used unless the clinic is one conducted by a tuberculosis sanatorium or other hospital.

In all probability there is one physician and two nurses in attendance at each clinic session and there are two sessions weekly, both day sessions. The clinic nurses do not administer tuberculin but they are probably responsible for reading the results of tuberculin tests. Generally speaking, pneumothorax treatments are not given at the clinic, nor are other surgical procedures practised. Neither is heliotherapy in use in the clinic.

The chances are that no special experimental or research work is under way in the clinic, nor is the clinic used as a formal teaching centre. The clinic itself or the agency conducting the clinic carries on an educational program, using one or more of a variety of educational methods including the routine distribution of printed instructions and other literature. There is nursing supervision of clinic patients in the home, this part of the clinic program being carried on by the nurses attached to the clinic, alone or with the coöperation of the personnel of one or more other agencies.

The chances are that the clinic is supported in whole or in part by

public funds. The chances are about equal that the medical personnel hold salaried positions and so are not paid specifically for their clinic work which represents only a part of their duties, and that they are paid specifically for their clinic work, in which case the hourly rate of payment amounts to something like $3.00. The annual salary of the clinic nurses is probably between $1,500 and $1,800.

The Itinerant Clinic

Those clinics classified as itinerant seem to be divided roughly into two rather distinct types, one operated on a local basis by a local agency and the other operating on a state-wide, in some cases a limited state-wide basis, by a state agency. The service rendered by the former type of itinerant clinic closely resembles the service rendered by the permanent clinic in that regular sessions are generally held at fixed stations in the territory covered. The latter type is more likely to furnish a service irregular in nature both as to place and intervals between sessions.

Like the typical permanent clinic, the itinerant one may be conducted by any one of a variety of agencies. It is even more likely to have been a development of the more recent years than the typical permanent clinic. Its purpose is almost wholly diagnostic and again like the permanent clinic it renders its service without charge to the applicant irrespective of economic considerations. It is more likely, however, to require the referral of applicants by a physician than is the typical permanent clinic.

The chances are that X-ray apparatus is an actual part of the itinerant clinic's equipment more often than in the case of the permanent one, but fluoroscopic equipment is found less often. Laboratory service is furnished almost entirely by outside agencies. Tuberculin and lipiodol are used as diagnostic aids about as frequently as in the case of the permanent clinic.

One physician and two nurses are probably in attendance at each clinic session. The clinic nurses probably do not administer tuberculin, but the chances are about equal that they are responsible for reading the reactions. Generally speaking, pneumothorax treatments are not included in the service rendered; in fact, treatment measures of any sort are far less common than in the typical clinic of a permanent nature.

Almost no experimental and little research work is carried on by this type of clinic, but it is probable that a special effort is made to have the

clinic serve as a centre for informal teaching, for visiting physicians especially. Again, like the typical permanent clinic, it does educational work using one or more of a variety of methods, including the distribution of printed matter and talks to both patient groups and more general local groups. There is follow-up and nursing supervision of the clinic patients in the home, but it is more likely to be under the direction of some agency other than the one conducting the clinic than is the case with the permanent clinic.

It is more than likely that this type of clinic is supported in whole or in part by public funds. For the most part the medical personnel is salaried so that it is not possible to compute an hourly rate of payment. The annual salaries of nursing personnel are approximately the same as those paid to nurses attached to permanent clinics.

The Occasional Clinic

This type of clinic is perhaps best characterized by its sporadic activity and its lack of the more refined aids to diagnosis. For example, X-ray and fluoroscopic equipment will almost never be a part of its equipment and, furthermore, it is more often not conveniently available than in the other two types of clinics. Tuberculin is less frequently used and lipiodol almost never.

While it is true that there are likely to be a greater number of physicians, nurses, and other personnel in attendance at the clinic sessions, it is doubtful whether all take an active part in the actual conduct of the clinic, and more likely than not, much of the "other" personnel will be volunteer clerical helpers. There is little follow-up and supervision in the home by any of the personnel attached to the clinic, whatever is done in this connection being almost wholly assigned to the family physicians and the personnel of existing local agencies in the communities served by the clinic..

This type of clinic has little or no opportunity for carrying on any kind of an extensive educational program and still less opportunity for carrying on any special experimental or research work. It is quite likely that the physician or physicians making the examinations serve without remuneration. It is also likely that the expense of conducting the clinic, usually a small amount, is borne in whole or in part by a tuberculosis association.

STATISTICAL SUMMARY

In concluding this analysis it seems desirable to present certain estimates which will represent roughly the volume of service rendered by all tuberculosis clinics in the United States. Assuming that the completed schedules which were received, and which have been used as the basis of this analysis, constitute a representative sample of all existing clinics, and assuming, further, that the statistical data given in connection with certain items on the schedule are proportionately representative of all existing clinics, it is possible to arrive at the following estimates of the amount of service rendered annually in the United States. Clinic sessions number well over 100,000; between 500,000 and 600,000 sputum tests are made; and a similar number of X-ray films, probably close to 600,000, are taken. More than 1,000,000 individuals make approximately 2,500,000 visits to the clinics; an even greater number of home visits, roughly 3,000,000, are made by the clinic and other personnel. Annual expenditures for carrying on the activities of the clinics are between $7,000,000 and $8,000,000, from funds obtained from both public and private sources.

VIRULENCE OF BOVINE TUBERCLE BACILLI[1, 2]

Variations Depending on the pH of the Culture Medium

KENNETH C. SMITHBURN

The experiments discussed in this and the two succeeding papers are a part of a program of investigation undertaken with the hope of determining what factors associated with tubercle bacilli are responsible for their capacity to survive and multiply in the animal body and to produce progressive disease. In the first paper it will be shown that, according to conditions adopted for cultivation of the organisms, their virulence may be retained for prolonged periods, or attenuation may be brought about *in vitro* at will. In the second paper it will be demonstrated that the histopathology of the disease induced experimentally varies according to the virulence of the organisms inoculated. And in the third report the changes occurring in the blood cells in rapidly advancing tuberculosis will be compared with those occurring when the lesions are slowly progressive or retrogressive.

The phenomenon of bacterial dissociation, the significance of which was first brought to light by Arkwright (1 to 3), De Kruif (4 to 6), and Northrop and De Kruif (7, 8) has been abundantly shown to apply to tubercle bacilli. Although morphological variants were observed in cultures of *Mycobacteria* as early as 1913 (9, 10), the group of investigators at Trudeau were first to study dissociation of tubercle bacilli from warm-blooded animals (11 to 20). In studies of bovine tubercle bacilli, Petroff and Steenken (11, 15, 16) observed two types of colonies in cultures grown on gentian-violet-egg-veal medium and noted that the addition of sodium taurocholate to this medium facilitated the differentiation of the colonies. One type of colony was round, moth-ball-like and nongranular (S), while the other was flat and spreading (R). The S colonies were easily suspended in saline and proved to be virulent, while the R colonies were difficult to suspend and were attenuated (16).

[1] Presented in part at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

[2] From the Laboratories of The Rockefeller Institute for Medical Research, New York City.

These studies were confirmed and extended by Reed and his associates (21 to 25). A number of others have studied the dissociation of tubercle bacilli (26 to 36), but the interpretation of results was not wholly in agreement. For example, the workers at the Institut Pasteur (29 to 34) found the smooth colonies of bovine tubercle bacilli to be virulent when first isolated, but they observed loss of virulence on subcultivation. The colonies which they designated R were found to be virulent and to remain virulent on subcultivation. These apparent discrepancies in results will be taken up in the Discussion.

Our own studies on dissociation of *Mycobacteria* were begun in 1934. The first study (37) indicated that S colonies were sensitive to acid and alkali and that they occurred in greatest numbers when treatment of infected tissues with these agents was avoided. This suggested that the pH of the culture medium might also be a factor of importance in determining the form and virulence of colonies which developed; and this proved to be the case (38 to 41). The form of colonies which developed in cultures of human, bovine, and avian tubercle bacilli was found to be markedly influenced by the pH at which the organisms were grown (40, 41). It had already been demonstrated by Steenken, Oatway and Petroff (18) that cultivation of R colonies of the H37 human strain on acid medium favored stabilization of this attenuated form, while cultivation of the S form on alkaline medium aided stabilization of this, the more virulent colonial variant. However, prior to 1935 (38, 40, 42), to our knowledge, it had not been observed that the initial pH of the culture medium had an effect on the colony form of tubercle bacilli, or that colonial variation could be initiated by altering the pH of the medium. We observed (41) that the cultivation of bovine tubercle bacilli in successive generations at pH 6.0 produced a maximum of R colonies; at pH 6.4 to 6.8, the colonies were predominantly smooth; and at pH 7.2 they were flat, spreading and finely granular. The latter were designated as intermediate forms. Since these experiments were reported, we have continued to make transplants of various strains of tubercle bacilli in series on medium adjusted to these pH values. The cultures of bovine tubercle bacilli grown at pH 6.0, 6.8 and 7.2 have shown no significant deviation from the morphology previously described (41). But cultures grown at pH 6.4 have shown progressively greater numbers of granular colonies and have come to resemble more closely the cultures grown at pH 6.0 than those grown at pH 6.8. The present report deals with various tests of the virulence of these cultures.

MATERIALS AND METHODS

The bovine tubercle bacillus, Strain 39, isolated in 1932 by the late Dr. Theobald Smith, has been used most extensively in these studies. This strain proved to be one of the four most virulent of twelve strains studied in previous experiments (39, 41). The cultures used in the present experiment were grown at four different pH values, namely, pH 6.0, 6.4, 6.8 and 7.2, on Corper's glycerol-egg-yolk medium (43) with either Congo red or India ink added to facilitate visual contrast. Colony selection was never used, nor were suspensions filtered prior to seeding subcultures. In this way the influence only of the pH of the medium was permitted to exert an effect on colony form or virulence. The method of derivation of the cultures has previously been described at length (41), as have the colonial characteristics. A single experiment was done employing the bovine strain 32, also isolated by Theobald Smith and known to be markedly attenuated (39, 41).

Animals used, methods of inoculation, etc., will be discussed under individual experiments.

All animals were weighed at frequent intervals. All were housed under identical conditions, received the same diet, were fed by the same attendant, and none was subjected to any procedure which might have influenced the course of disease. At death each animal was closely examined and records were made as to the extent and appearance of the lesions. In determining the lung weights of intravenously inoculated rabbits, the heart, lungs and trachea were removed as a unit, the heart and mediastinal structures were dissected away, the trachea was cut off in a line connecting the tip of the anterior lobes, and the lungs were dried on gauze before weighing. Blocks of tissue from various viscera were fixed in Helly's fluid (except brains which were fixed in 10 per cent formalin), and paraffin sections were prepared in the usual manner. As routine, sections were stained in haematoxylin and eosin, and for bacteria with anilin fuchsin, haematoxylin and light green (F. S. Grübler). Sections of lung, spleen, and bone marrow were examined for bacteria in animals inoculated intravenously, and of brain, spleen, and lung in animals inoculated intracerebrally.

Tabulation of extent of lesions: At autopsy the extent of tuberculous lesions in lymph nodes, thoracic and abdominal viscera, and femoral bone marrow was estimated for each animal and was recorded as 0 to ++++ for each tissue. Later, similar estimates were made from

microscopical sections. The sum of the data for each tissue gave a figure for each animal, and the sum of figures of all the animals of a group gave a figure representing the extent of lesions in the group. Data for gross lesions and those for microscopical lesions were kept separate. These data are expressed in tables 1, 5 and 7 as "units" of macroscopical or microscopical tuberculosis. Sections of lung, spleen, and femoral bone marrow of each animal, appropriately stained, were examined for tubercle bacilli. The number of bacilli was recorded as 0 to ++++; + indicated a single bacillus, or less, per oil field in areas of greatest bacterial population, ++ indicated not more than ten per oil field, +++ indicated between eleven and forty per oil field, and ++++ indicated any number greater than forty per oil field (often too numerous to be counted) in the most densely populated areas. In addition to bone marrow, spleen, and lung, whenever the heart or the Peyer's patches of the intestine showed macroscopical tuberculosis, sections of these tissues were examined for acid-fast bacteria, and these data were recorded with the total for the animal concerned. The values for each tissue of an animal were added, then the values for all the animals of a group, and the latter sum is expressed as "units" of acid-fast bacilli in tables 1, 5 and 7.

FIRST EXPERIMENT

Procedure: In this experiment, a preliminary test of the virulence of cultures of bovine organisms grown at various pH values, sixteen rabbits, English-lilac, hybrid females, bred at the Rockefeller Institute and varying in age from 8 to 13 months and in weight from 2,640 to 3,980 gm., were divided into four groups of four each. The groups were as nearly alike as possible in regard to individual and group weights. Four cultures of the bovine strain 39, third generation grown at pH 6.0, 6.4, 6.8 and 7.2 respectively, each of the same age (30 days), were used for inoculation, each group of rabbits being inoculated with one of the four cultures. Suspensions of each culture were prepared by grinding a weighed quantity of bacilli in a sterile porcelain mortar with saline, so that 1.0 cc. contained 1.0 mgm. of microörganisms. Dilutions were then prepared so that 1 cc. of suspension contained 0.01 mgm. of bacilli, and each rabbit was inoculated intravenously in the marginal vein of the right ear with 1.0 cc. of this suspension. Smears prepared with one loopful of the original suspensions showed no appreciable differences in number of microörganisms present. However, the bacilli grown at pH 6.8 and pH 7.2 were a little longer than those grown at pH 6.0 and

6.4, and there was slightly less tendency to clumping in the suspension of microörganisms grown at pH 6.8.

This was a preliminary experiment, the result of which could not be predicted, so that, when animals of the group inoculated with the culture grown at pH 6.8 began to die, individuals of the other groups were sacrificed for comparison. The two survivors of the group inoculated with the culture grown at pH 6.0 were sacrificed to terminate the exper-

TABLE 1

Relative extent of tuberculosis and number of tubercle bacilli in lesions of four groups of animals inoculated with cultures of bovine tubercle bacilli, Strain 39, grown through three generations at different pH values

ANIMAL NUMBER*	CULTURE GROWN AT pH	DIED OR KILLED	DAYS AFTER INOCULATION	UNITS MACROSCOPICAL TUBERCULOSIS TOTAL	UNITS MICROSCOPICAL TUBERCULOSIS TOTAL	UNITS TUBERCLE BACILLI TOTAL
3793	6.0	K	40			
3805	6.0	K	41	37	38	6
3792	6.0	K	121			
3803	6.0	K	121			
3794	6.4	K	40			
3795	6.4	K	41	82	80	23
3806	6.4	D	56			
3796	6.4	D	61			
3804	6.8	D	31			
3799	6.8	D	40	88	85	27
3797	6.8	K	41			
3798	6.8	D	56			
3791	7.2	K	40			
3801	7.2	K	41	59	56	13
3802	7.2	D	64			
3800	7.2	D	121			

* These are serial numbers used in this laboratory over a period of years.

iment at the time of the death of the last animal of the group inoculated with the culture grown at pH 7.2.

A duplicate series of sixteen similar animals was divided into four groups of four each and inoculated intravenously with 0.1 mgm. of the corresponding cultures of the avirulent[3] bovine strain 32 (39), grown at

[3] It must be emphasized that each of the strains and variants employed in this and in our preceding studies was a nonchromogenic, slow growing, acid-fast microörganism. The avirulent strain 32 and the attenuated variants of strain 39 were therefore wholly unrelated to saprophytic, acid-fast bacteria.

pH 6.0, 6.4, 6.8 and 7.2. The cultures of this strain presented in each instance colonies closely resembling those of the corresponding culture of the virulent bovine strain 39, grown on medium having the same pH (41).

Results: Since some of the animals were killed, data on survival time were not comparable, but the studies of the lesions revealed sharp differences in the virulence of the microörganisms. The data on time of death and extent of lesions, together with estimates of the number of tubercle bacilli in the lesions of this group, are shown in table 1. From these data it may be seen that the cultures of bovine strain 39 grown at pH 6.4 and at 6.8 were of approximately equal virulence, that grown at pH 7.2 was slightly attenuated, and that grown at pH 6.0 was rather markedly attenuated. The latter culture was composed chiefly of granular R colonies. The cultures grown at pH 6.4 and pH 6.8 were composed chiefly of S colonies (41, figures 1 & 2), and the culture grown at pH 7.2 was composed almost wholly of flat, spreading colonies. Thus the R seemed to be the attenuated, the S the virulent, and the flat, spreading to be the next most virulent. The second experiment further elaborates this point.

Results in the duplicate series of animals inoculated with corresponding cultures derived from the avirulent bovine strain 32 (39, 41) may be summarized in a few words. None of the animals died, none exhibited progressive tuberculosis, and the lesions found when the animals were sacrificed were in every instance minimal. This demonstrated clearly that all colonial variants derived from avirulent strains were avirulent, as was to be expected.

SECOND EXPERIMENT

Procedure: The rabbits used in this experiment were all pure stock New Zealand reds bred at the Rockefeller Institute. Forty-two animals from twenty-two litters were divided into four groups of ten each, and two rabbits were reserved for a special purpose. Divisions were made so that there was equal distribution as regards age, sex, weight and numbers of each litter. These precautions were taken in order to have the groups as nearly comparable as possible and thereby to eliminate variations in susceptibility. The data concerning age, sex, weight and litter mates of animals in the four groups are included in table 2.

The cultures used for inoculation were bovine tubercle bacilli, Strain 39, organisms of the fifth generation grown at pH 6.0, 6.4, 6.8 and 7.2.

TABLE 2

Division of animals into groups according to age, sex, weight, litters, and inoculum received

ANIMAL NUMBER	BORN	WEIGHT	SEX	LITTER MATE OF RABBIT NUMBERS	INOCULATED WITH CULTURE GROWN AT pH	ANIMAL NUMBER	BORN	WEIGHT	SEX	LITTER MATE OF RABBIT NUMBERS	INOCULATED WITH CULTURE GROWN AT pH
	1936	*gm.*					*1935*	*gm.*			
4280	Mar. 2	3960	F		6.0	4281	Feb. 8	4500	F		6.4
4284	Mar. 24	3660	F	4283, 4290	6.0	4289	Feb. 6	3660	F		6.4
4292	Feb. 12	3460	M	4296, 4300	6.0	4293	Mar. 24	2700	M	Same age as 4283, 4284, 4290	6.4
4299	Mar. 29	3280	F		6.0	4295	Apr. 1	3460	F	4294	6.4
4286	Apr. 25	3820	F	4282, 4287, 4288	6.0	4365	June 9	2780	M		6.4
4358	May 7	2960	M	4349, 4361, 4363	6.0	4287	Apr. 25	3520	F	4282, 4286, 4288	6.4
4353	May 17	3260	F	4352, 4354	6.0	4349	May 7	3540	M	4358, 4361, 4363	6.4
4346	May 17	3440	M	4350, 4351, 4362	6.0	4350	May 17	3560	M	4346, 4351, 4362	6.4
4360	May 25	3400	F	4357	6.0	4357	May 25	4140	F	4360	6.4
4348	May 15	3200	M	4364	6.0	4366	June 10	3080	F	4355	6.4
Average.....		3444				Average.....		3494			
4290	Mar. 24	3000	M	4283, 4284	6.8	4283	Mar. 24	3480	F	4284, 4290	7.2
4294	Apr. 1	3400	M	4295	6.8	4291	Feb. 28	3200	M		7.2
4296	Feb. 12	4120	F	4292, 4300	6.8	4298	Mar. 26	3460	M		7.2
4297	Feb. 13	3940	F		6.8	4300	Feb. 12	4220	F	4292, 4296	7.2
4282	Apr. 25	3260	F	4286, 4287, 4288	6.8	4288	Apr. 25	3220	F	4282, 4286, 4287	7.2
4361	May 7	3080	M	4349, 4358, 4363	6.8	4363	May 7	3040	M	4349, 4358, 4361	7.2
4355	June 10	3120	F	4366	6.8	4364	May 15	3240	F	4348	7.2
4352	May 17	3400	M	4353, 4354	6.8	4354	May 17	3660	M	4352, 4353	7.2
4351	May 17	3560	M	4346, 4350, 4362	6.8	4368	June 10	3860	M	Same age as 4355, 4366	7.2
4356	May 31	3920	F	4359	6.8	4359	May 31	3480	F	4356	7.2
Average.....		3480				Average.....		3486			

The cultures were of the same age, 28 days, and one group of ten animals was inoculated with each culture. Suspensions were prepared in the same manner as in the previous experiment. The dose of each culture was in every instance 0.01 mgm. in 1.0 cc. sterile saline, inoculated into the marginal vein of the right ear, except that rabbits R 4285 and R 4362 each received 0.1 mgm. of the attenuated culture grown at pH 6.0. Before discussing the results of this experiment, it must be emphasized that, following the previous experiment, the cultures grown at pH 6.4 began to show numerous R colonies, while the cultures grown at other pH values remained constant in their colonial morphology.

Results: (*1*) *Survival time and change in weight:* Of the ten animals receiving 0.01 mgm. of culture grown at pH 6.0, one died with an intercurrent, nontuberculous pneumonia at 65 days and showed minimal tuberculosis. The nine remaining animals survived and were killed between the 161st and 183rd day after inoculation, at which time all appeared well. The average survival time was 164.4 days. From the beginning of the experiment to the end, four of these animals lost weight (20 to 380 gm.), while six gained (from 60 to 580 gm.). The net change in weight of the ten animals was a gain of 1,470 gm., or an average gain of 147 gm. per animal. These results are shown in table 3.

Six of the ten animals receiving a similar dose of microörganisms grown at pH 6.4 died between the 67th and 141st day, while the remainder were killed between the 161st and 180th day. The average survival time was 130.3 days. Each of the ten animals lost weight, the minimum being 40 gm., the maximum 1,100 gm., the total 4,920 gm., and the average 492 gm. per animal.

Survival time was shortest in the ten animals receiving microörganisms grown at pH 6.8. All died from the disease between the 38th and 103rd day and only one lived over 72 days. The average survival was 58.5 days. Again each animal lost weight, the amount varying from 180 to 740 gm., the total being 4,700 gm., and the average per animal was 470 gm. This wasting is approximately equal to that observed in the preceding group of animals. It will be shown that, while the emaciation was slightly less, the lesions were more extensive, so that acuity of disease and emaciation did not go hand in hand. This was further elucidated by the data which follow.

Of the animals inoculated with microörganisms grown at pH 7.2, nine died and the tenth was killed when moribund. The first death occurred on the 63rd day and the last on the 122nd. The average sur-

vival time was 89.6 days. Each of the ten animals lost weight, the amount varying from 280 to 1,520 gm., the average being 766 gm. Thus, while these animals survived on the average a full month longer than the preceding group, the final loss of weight was greater.

Of the two animals inoculated with the tenfold dose of attenuated culture grown at pH 6.0, neither died. One was killed at 162 and one at 180 days. One lost weight and the other gained, the average being a net loss of 45 gm.

The data showing the survival time and the changes in weight are recorded in table 3.

Thus, on the basis of survival time, the culture grown at pH 6.8 was most virulent, that grown at pH 7.2 next most, that grown at pH 6.4

TABLE 3

Survival time and loss of weight in animals inoculated with cultures of bovine tubercle bacilli, Strain 39, grown through five generations at different pH values

NUMBER OF ANIMALS	CULTURE GROWN AT pH	NUMBER DIED	NUMBER KILLED	AVERAGE SURVIVAL	AVERAGE NET CHANGE IN WEIGHT§
				days	*gm.*
10	6.0	1*	9	164.4	+147
10	6.4	6	4	130.3	−492
10	6.8	10	0	58.5	−470
10	7.2	10‡	0	89.6	−766
2†	6.0	0	2	171.0	−45

* Pneumonia and minimal tuberculosis.

† These two animals received tenfold the inoculating dose given to the other four groups.

§ + and − indicate gain or loss in weight.

‡ One killed when moribund.

was definitely attenuated, and that grown at pH 6.0 was markedly attenuated. The latter was made especially evident by the finding that a tenfold dose failed to kill either of two animals in 5 to 6 months.

(2) *Weight of lungs and weight of spleen as expressions of extent of tuberculosis:* The occurrence of splenomegaly in rabbits inoculated intravenously with virulent tubercle bacilli is well known. Likewise but little experience is necessary before it becomes obvious that the lungs increase in weight during a progressive tuberculous infection. We therefore sought to determine whether or not animals inoculated with virulent tubercle bacilli would show greater changes in the weight of spleens and lungs than animals inoculated with an identical dose of attenuated microörganisms, and to ascertain if the weight of lungs and spleen was correlated with the extent of tuberculous lesions.

Brown, Pearce, and Van Allen (44) showed that in animals weighing between 3,000 and 3,500 gm. (comparable in size to animals used in this experiment) the spleen weight varied from 0.93 gm. to 1.89 gm. The mean of these figures, for comparison with the data in table 4, is 1.32 gm. or, expressed as per cent of body weight, it is 0.042. Using these figures as a basis for comparison, it may be seen from table 4 that the spleen weight in each group of animals was greater than normal. The increase in the group inoculated with 0.01 mgm. of culture grown at pH 6.0 was on the order of 50 per cent (0.042 per cent body weight to 0.63 per cent body weight). But the animals inoculated with the same dose of microörganisms grown at pH 6.4 exhibited spleens weighing approximately twice that of those inoculated with the more attenuated culture; those inoculated with culture grown at pH 7.2 had spleens still larger, while those inoculated with the most virulent culture, grown at pH 6.8, had spleens averaging 7.32 gm., or 0.237 per cent body weight. The latter figures are more than five times the normal.

No data on normal weight of lungs of rabbits being available, we obtained the following from fifteen rabbits. Included in the group were one chinchilla, four New Zealand reds, and ten English-lilac hybrids. Body weight varied from 1,480 gm. to 2,980 gm. and lung weight, expressed as per cent of body weight, from 0.342 to 0.525 per cent, with an average of 0.428. The four New Zealand reds weighed from 2,660 to 2,980 gm. and their lungs represented from 0.342 to 0.369 per cent of body weight. Thus, as a rule, the weight of the lungs in normal rabbits represents less than 0.5 per cent of the body weight.

In the animals inoculated with bovine tubercle bacilli grown at pH 6.0, the lungs, on the average, represented 0.69 per cent of body weight, a definite increase over normal, but remarkably less than in the other three groups inoculated with the same dose of microörganisms grown at different pH values. Table 4 shows that those receiving culture grown at pH 7.2 showed the greatest increase in lung weight, despite the fact that the bacilli grown at pH 6.8 killed more quickly. But it must be considered that these animals lived on the average a month longer than those inoculated with microörganisms grown at pH 6.8, and that the flat, spreading colonies (pH 7.2) produce fatal, progressive tuberculosis. The approximate sevenfold increase in weight of the lungs in these two groups of animals, representing as it did the weight of the pulmonary tubercles, is quite striking when compared with the figure obtained in animals inoculated with the attenuated culture (pH

6.0). The weights of lung and spleen, therefore, express in a rough way the virulence of the microörganism, but still more accurately the extent of disease in those viscera. The two animals inoculated with a tenfold dose of the attenuated culture (pH 6.0) exhibited lungs which weighed slightly, but not significantly less than those inoculated with the smaller dose of the same culture. This demonstrated conclusively, as did the data on survival time, that the differences in survival time, lung weight, etc., between the groups inoculated with culture grown at pH 6.0 and those with the culture grown at pH 6.8, were not likely due to differences in number of bacilli inoculated, but rather to inherent differences in the properties of the bacteria.

(*3*) *Extent of lesions and number of tubercle bacilli in lesions:* Lesions were most extensive in the group of animals inoculated with the culture

TABLE 4

Weight of spleen and weight of lungs in groups of animals inoculated with bovine tubercle bacilli, Strain 39, grown through five generations at different pH values

NUMBER OF ANIMALS	INOCULATED WITH CULTURE GROWN AT pH	SPLEEN WEIGHT AVERAGE	SPLEEN PER CENT BODY WEIGHT AVERAGE	LUNGS PER CENT BODY WEIGHT AVERAGE
10	6.0	2.22	0.063	0.693
10	6.4	4.11	0.137	2.205
10	6.8	7.32	0.237	3.030
10	7.2	4.66	0.172	3.330
2*	6.0	3.75	0.115	0.525

* These two animals received tenfold the inoculating dose given to the other four groups.

grown at pH 6.8 (table 5). Not only were the lesions in lung, spleen, lymph nodes, etc., more extensive, but there were frequently tubercles in the adrenals, heart and gastrointestinal tract, situations less frequently involved, if at all, in the other groups. The animals inoculated with culture grown at pH 7.2 showed next most extensive lesions, while lesions were fewer but still extensive in the group inoculated with the culture grown at pH 6.4, and fewest in number in those receiving microorganisms grown at pH 6.0. Furthermore, the two animals inoculated with the tenfold dose of bacilli grown at pH 6.0 showed fewer lesions per animal than any of the other groups except those receiving the smaller dose of the same culture, again demonstrating that the differences noted were due to properties of the microörganisms inoculated rather than to minor differences of dosage which may have occurred.

In every instance there was a parallelism between the extent of lesions

in a group of animals and the relative number of tubercle bacilli in those lesions (table 5). The animals inoculated with culture grown at pH 6.8 showed the most numerous tubercle bacilli in their lesions, those inoculated with culture grown at pH 6.0 showed fewest, and those in the other groups occupied intermediate positions parallel to the extent of tubercles present in the tissues. Sections from the animals inoculated with the attenuated culture (pH 6.0) showed only a very few tubercle bacilli or none at all. In the group inoculated with the culture grown at pH 6.8, tubercle bacilli were very numerous and records of +++ or ++++ were the rule rather than the exception. These facts were of particular interest since the weighed dose of bacilli injected was the same.

TABLE 5

Relative extent of tuberculous lesions and relative number of tubercle bacilli in lesions of groups of rabbits inoculated with cultures of bovine tubercle bacilli, Strain 39, grown through five generations at different pH values

NUMBER OF ANIMALS	INOCULATED WITH CULTURE GROWN AT pH	TOTAL UNITS MACROSCOPICAL TUBERCULOSIS*	TOTAL UNITS MICROSCOPICAL TUBERCULOSIS*	TOTAL UNITS TUBERCLE BACILLI IN LESIONS*
10	6.0	27	55	3
10	6.4	136	200	45
10	6.8	196	263	89
10	7.2	155	224	77
2†	6.0	12	23	4

* Manner of obtaining data and definition of "unit" are included in the text.

† These two animals received tenfold the inoculating dose given to the remaining four groups.

The foregoing data again indicate that the culture grown at pH 6.8 (predominantly smooth colonies) was the most virulent, while that grown at pH 6.0 (chiefly rough colonies) was the most attenuated. Furthermore, it is clear that the culture grown at pH 7.2 (flat, spreading colonies) was as virulent as in the preceding experiment but slightly less virulent than the culture grown at pH 6.8. Lastly, the culture grown at pH 6.4 (rough and flat, spreading colonies) was considerably attenuated, showing that the change in colonial morphology occurring in the fourth and fifth generations (smooth to granular) was associated with a loss of pathogenic properties.

(*4*) *Relation of rate of growth in vitro to virulence:* We have performed no controlled experiments to determine the relative rate of growth of virulent and attenuated lines of cultures. However, it has invariably

been noted that most vigorous growth of the bovine strain 39 occurred in the line of cultures grown at pH 6.0, and that growth was least vigorous in cultures grown at pH 6.8 and pH 7.2. The time of appearance of colonies was usually about the same, but the total amount of growth was three to eight times greater (by weight) at pH 6.0 than at pH 6.8. Since the latter showed much more growth *in vivo*, it appears that there is an inverse relation between *in vitro* growth and virulence.

THIRD EXPERIMENT

Recent studies (45 to 51) have emphasized the value of a hitherto little used route for inoculation in studies on tuberculosis, namely, the intracerebral. Boquet and Broca (45) tested a number of strains of tubercle bacilli by this route. They found that avirulent strains such as BCG, or killed bacilli, did not induce fatal disease, whereas virulent microörganisms did. Feldman used this route of inoculation in a series of significant studies of lesions induced in dogs by avian tubercle bacilli (47 to 49) and in chickens by mammalian type microörganisms (50, 51). However, we (46) found that virulent microörganisms injected by this route into susceptible animals induced acute meningoencephalitis which was rapidly fatal, the incubation period and survival time being dependent on the dose inoculated. Quantitative biological titrations were shown to be possible by this method since animals inoculated with a given dose of the same virulent strain survived about the same length of time. Moreover, it was shown (46) that inoculation of attenuated strains caused death irregularly and only after a prolonged period. In the present experiment this method was employed as a further check on the virulence of microörganisms grown at various pH values.

Forty-eight healthy male guinea pigs weighing from 360 to 540 gm. (average 420 gm.) were divided into twelve groups of four each, depending on weight. Animals heavier and lighter than the average were distributed in each group and the total weight of each group was made as nearly as possible the same. The animals were isolated for a week prior to inoculation to detect any which might have been ill.

Cultures of bovine tubercle bacilli, Strain 39, grown through seven generations at pH 6.0, 6.4, 6.8 and 7.2, were used for inoculation. The cultures were each of the same age (37 days). Suspensions of each culture were prepared as in the previous experiments, and then three dilutions of each suspension were made so that 0.1 cc. contained 0.01 mgm., 0.000,1 mgm. and 0.000,001 mgm. Smears were prepared from a

single loopful of each original suspension (1 cc. = 1 mgm.) and were stained by the Cooper method. The microörganisms grown at pH 6.0 and pH 6.4 were short and showed a moderate tendency to clump. The microörganisms grown at pH 6.8 and 7.2 showed less tendency to clump, and those grown at pH 7.2 were, on the average, a little longer and slightly less well stained. The number of bacilli present appeared to be about two times as great in the case of microörganisms grown at pH 6.8 and 7.2. Non-acid-fast forms were not found in any of the smears.

Each group of four animals was then inoculated with one dose of one of the four cultures. Inoculations were done under ether anaesthesia by the method described previously (46). The twelve groups of animals were submitted to no other experimental procedure. One animal died of intercurrent pneumonia 8 days after inoculation and was excluded from the experiment.

Results: (*1*) *Survival time:* Sharp differences were noted in the survival time of the various groups of animals, depending upon the virulence of the culture and the dose of microörganisms inoculated. The data on survival time of the various groups are recorded on chart 1.

Chart 1 shows the average survival time in days of twelve groups of four animals inoculated intracerebrally with various doses of microorganisms grown at four different pH values. S preceded by a figure in the unshaded portion of a column indicates the number of survivors in that group.

Table 6 includes the data on survival time of individuals. Each figure in table 6 indicates the number of days between inoculation and death in one guinea pig. From the two last columns to the right it may be seen that a hundredfold dilution of dosage of a given culture allowed an increase of about 8 days in the average survival time of a group of animals. It will also be noted (chart 1 and table 6) that in animals inoculated with microörganisms grown at pH 6.8 the survival time was shorter than in the corresponding group inoculated with the same dose of any other culture. The difference between the average survival time of animals inoculated with culture grown at pH 6.8 and of those inoculated with bacilli grown at pH 7.2 was approximately 4 days for any given dose of bacilli, or roughly one-half the difference due to a hundredfold dilution of dosage of either culture. The animals inoculated with culture grown at pH 6.4 showed still greater average survival, and one animal receiving the 10^{-6} mgm. dose survived. Survival time was greatest in the three groups of animals inoculated with

microörganisms grown at pH 6.0. Moreover, one animal receiving 0.01 mgm., two animals receiving 0.000,1 mgm., and all animals receiving 0.000,001 mgm. of this culture survived and are apparently normal, 365 days following inoculation.

The data in table 6 are interesting from another standpoint. It will be noted that, with a large dose of virulent microörganisms, the animals all died at about the same time, resistance being apparently over-

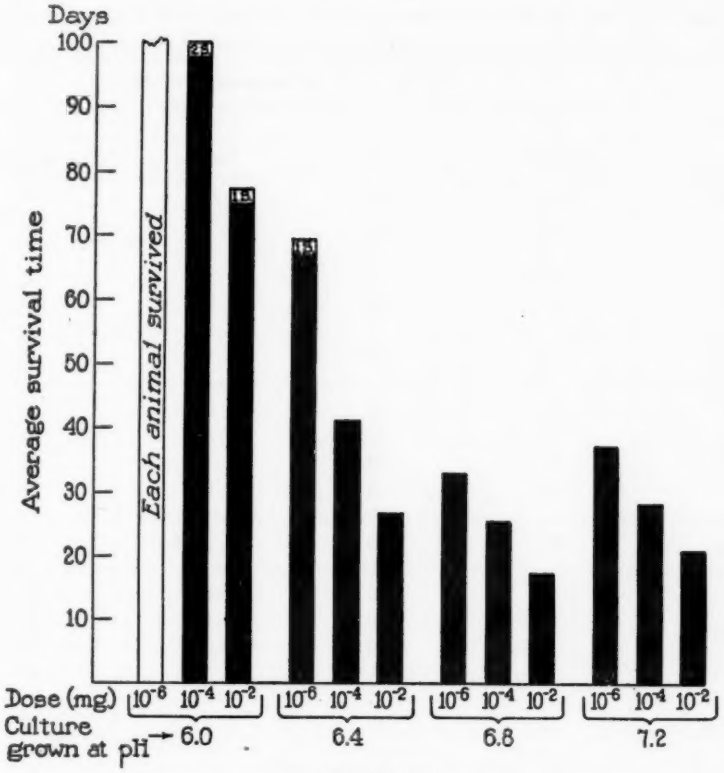

CHART 1

whelmed. With minimal doses of the same microörganism there was greater variation in individual survival time, individual resistance having opportunity to express itself. With large doses of attenuated bacilli resistance of the host again played an important part and there was considerable variation in survival time of different individuals. And lastly, with minimal doses of attenuated microörganisms resistance played the dominant part and there were no deaths. This experiment,

therefore, gave a clear-cut picture of the interplay of the two factors: host resistance and virulence of the microörganism.

(*2*) *Extent of tuberculous lesions and number of tubercle bacilli in them:* In guinea pigs inoculated intracerebrally we have found (46) a minimum of macroscopical tuberculosis, so that gross autopsy surveys are less reliable in giving an accurate picture of the pathological process than

TABLE 6

Survival time in guinea pigs inoculated intracerebrally with cultures of bovine tubercle bacilli, Strain 39, grown through seven generations at different pH values

DOSE	INOCULATED WITH CULTURE GROWN AT pH			
	6.0	6.4	6.8	7.2
	Survival	Survival	Survival	Survival
mgm.	*days*	*days*	*days*	*days*
10^{-3}	43*	24	13	20
	56*	25	17	21
	126*	31	18	22
	S	X	21	22
Average.....	75	26.6	17.25	21.25
10^{-4}	95	32	24	22
	101	36	24	23
	S	39	25	28
	S	56	29	39
Average.....	98	40.75	25.5	28
10^{-5}	S	40	27	26
	S	70	32	33
	S	92	35	40
	S	S	38	49
Average.....	S	67	33	37

S indicates that the animal survived 365 days or longer.
X indicates that one animal of this group died 8 days after inoculation, from pneumonia.
* indicates complicating pneumonia discovered at autopsy.

microscopical studies. Often there are no formed macroscopical tubercles in the meninges, though microscopically the process is extensive. And metastatic visceral lesions are also frequently microscopical. In this experiment, therefore, we shall report only the results of the microscopical surveys. These estimates were made in the manner described under Methods.

Tuberculous lesions were most numerous and extensive in the groups of animals inoculated with cultures grown at pH 6.8 and pH 7.2 and usually, though not invariably, in the former of these two. They were invariably least extensive in the animals inoculated with microörganisms grown at pH 6.0. Data showing the extent of tuberculous lesions and number of tubercle bacilli in these lesions in the twelve groups of animals are recorded in table 7.

TABLE 7

Survival time, relative extent of lesions and relative numbers of tubercle bacilli in lesions of animals inoculated intracerebrally with bovine tubercle bacilli, Strain 39, grown through seven generations at various pH values

NUMBER OF GUINEA PIGS	CULTURE GROWN AT pH	DOSE	AVERAGE SURVIVAL	TOTAL UNITS TUBERCLE BACILLI IN LESIONS	TOTAL UNITS MICROSCOPICAL TUBERCULOSIS
		mgm.	days		
4	6.0	10^{-2}	75.0†*	3	13
3	6.4	10^{-2}	26.6	12	30
4	6.8	10^{-2}	17.25	24	38
4	7.2	10^{-2}	21.25	25	44
4	6.0	10^{-4}	98.0‡	2	7
4	6.4	10^{-4}	40.75	16	42
4	6.8	10^{-4}	25.5	23	42
4	7.2	10^{-4}	28.0	20	35
4	6.0	10^{-6}	S		
4	6.4	10^{-6}	67.0†	9	29
4	6.8	10^{-6}	33.0	22	43
4	7.2	10^{-6}	37.0	13	40

† Indicates one animal survived.
‡ Indicates two animals survived.
S indicates all animals survived.
* Each animal of this group exhibited complicating pneumonia at death.

The number of tubercle bacilli in sections of brain, spleen, and lung was likewise greatest in animals inoculated with cultures grown at pH 6.8 and 7.2, and least in animals inoculated with the culture grown at pH 6.0. That these differences could not have been due to differences in numbers of microörganisms inoculated is apparent from the fact that greater numbers of microörganisms were present after inoculation of 0.000,001 mgm. of culture grown at pH 6.8 than after inoculation of 10,000 times this dose of microörganisms grown at pH 6.0. The differences noted must, therefore, have been due to properties of the microorganisms.

DISCUSSION

The state of our knowledge concerning the relation between the colony form and virulence of tubercle bacilli is somewhat confused. This confusion is due largely to three facts: first, tubercle bacilli may and do grow in a wide variety of forms of colonies which the terms R and S are inadequate to describe; second, both virulent and avirulent tubercle bacilli produce various colonial variants; and third, there is a considerable lack of knowledge of the conditions necessary in order to preserve the virulence and stabilize the colony form.

As example of the colonial pleomorphism of tubercle bacilli and the inadequacy of present terminology, colonies which were flat, spreading and finely granular have been variously designated as S (16, 18, 21), R (32), intermediate (37, 39, 41), and Rv (19, 20). All the investigators referred to have found these colonies to be virulent when derived from a virulent parent strain. Therefore we have the confusing situation in which one author states that the S is the virulent form, another that it is the R which is virulent, while others use still another term.

Second, it is well recognized that avirulent tubercle bacilli produce various colonial variants (32, 35, 39), so that if a given form of colony derived from a virulent strain possesses the major pathogenic properties, it does not follow that the corresponding morphological variant derived from an avirulent strain will be virulent also. In our own experience and that of others (32, 35, 39), none of the colonial variants derived from avirulent strains demonstrate enhanced pathogenic properties. Smooth colonies of bovine tubercle bacilli may, therefore, be either virulent or attenuated, depending on whether they are derived from virulent or attenuated, undissociated strains (32, 35, 41), and granular colonies may also be either virulent or attenuated (16, 18 to 21, 32, 35, 41). Moreover, as we have previously shown (41), the colonial morphology of smooth forms undergoes change with aging and drying of the culture, and with the advent of secondary growth, so that a culture containing only smooth colonies after 3 weeks' incubation may appear essentially granular after 60 or 90 days' incubation. It is for these reasons, together with the fact that the methods which we have used do not exclude all save one colonial variant but merely cause a great predominance of that variant, that in presenting the present experiments we have laid greater stress on the pH of the medium than on the form of colony.

To demonstrate the third point made above, the lack of knowledge of cultural conditions necessary for stabilization of virulence and colony form, we have observed loss of virulence of an avian strain without change of colony form, rate of growth, or chromogenicity (39). Petroff observed loss of virulence of bovine S colonies without change in colony form (personal communication). And Birkhaug (32) reported obtaining smooth colonies of human and bovine type bacilli which were virulent soon after isolation in the dissociated state, but lost virulence after prolonged cultivation, and ultimately failed to produce progressive disease in susceptible animals.

This state of affairs has contributed to a discrepancy, more apparent than real, in the results obtained by the group at the Institut Pasteur, the workers at Saranac, and ourselves. In our work we have described three types of colonies from bovine strains and have designated them rough, intermediate and smooth. The present report shows that the rough are least virulent, the smooth most virulent, and the flat, spreading colonies next most virulent. But the workers in France found the S form, at first virulent, to be the attenuated and the R the virulent form. We believe this apparent discrepancy is due to two facts. First, the loss of virulence of the S form was possibly due to conditions of cultivation unsatisfactory for preservation of virulence. And second, it is our opinion that their R colonies (illustrated in 32, plate VI, figure 9) correspond to and are identical with those we have designated as intermediate. That this type of colony is virulent we are in agreement. But we have found in cultures grown at pH 6.0 an additional granular type of colony, more tortuous and having no tendency to spread, which we designated R (41), and which is the most attenuated variant. There is no disagreement between our results and those of Petroff and his associates, as the methods they employed included the selection of S and R forms, and they did not study flat, spreading variants of bovine tubercle bacilli. From this it is clear that there is greater concurrence of results than is at once apparent.

In the paper which follows it will be shown that the flat, spreading colonies, designated R by Birkhaug (32) and intermediate by ourselves (41), are not entities in the strictest sense but consist of a large proportion of virulent and a small proportion of attenuated elements. For this reason a term such as Rv ("v" indicating virulent), proposed by Steenken (19), would more explicitly express the properties of such microörganisms as regards both colony form and virulence. If such nomenclature were

adopted, our S colonies of bovine strain 39 would be designated Sv, and the R colonies from the same strain would be designated R_A ("A" indicating attenuated). Nevertheless, it should be repeated again that the flat, spreading colonies (Rv) are distinct in morphology from the R_A. the latter being coarsely granular, dry, tortuous, and showing no tendency to spread. It is highly probable that undissociated cultures of virulent tubercle bacilli are composed of a large proportion of Rv colonies, a small proportion of R_A colonies, and a negligible number of Sv colonies.

By alteration of environment alone we have found it possible to influence profoundly the form of colonies which develop in cultures of tubercle bacilli (41), and the present report shows that these differences in colony form are associated with differences in virulence of the microörganisms. In the case of a strain of bovine tubercle bacilli possessed of high virulence in the undissociated state, cultivation at pH 6.0 on Corper's medium gave rise to coarsely granular, tortuous (rough) colonies which were markedly attenuated. Cultivation of the same microörganisms on the same medium adjusted to pH 6.4 gave rise at first (three generations) to smooth colonies which were virulent, and subsequently (fourth to seventh generations) to coarsely granular colonies which were attenuated. Cultivation of the same microörganisms at pH 6.8 gave a maximum number of smooth colonies which retained their form and virulence through seven cultural generations. Cultivation of the same microörganisms on the same medium adjusted at pH 7.2 gave rise to flat, finely granular (spreading) colonies which in the third generation showed slight loss of virulence, but in the fifth and seventh generations showed no further loss of virulence and produced progressive, fatal tuberculosis in susceptible animals. Recent experiments have indicated that certain other strains do not become attenuated as quickly under these conditions as did the bovine strain 39.

It seems unlikely that the pH of the culture medium should be the sole factor controlling colony form and virulence of tubercle bacilli, especially since control of pH at any value in the range we have employed does not limit the growth exclusively to a single type of colony. However, by control of the pH of the medium, one can, within limits, control the colony form and preserve virulence (at least for a prolonged period), or at will induce attenuation of the microörganism. Whether the pH values we have found optimal for preservation of virulence, or for attenuation, apply for any and all media used for tubercle bacilli is not

known. We have employed for these studies only the glycerinated egg-yolk medium of Corper and Cohn (43).

From the data obtained it appears that weight of lungs and weight of spleen in uncomplicated tuberculous infection give a fair index of the extent of disease in those viscera. Survival time of comparable groups of animals is probably the best index of virulence. Especially was this evident in the guinea pigs inoculated intracerebrally. But the complete data, including lung and spleen weights, extent of lesions, number of acid-fast bacilli in the lesions, loss of weight, and survival time, each an expression of the pathogenic properties of the micro-organism, leave no doubt that the virulence of tubercle bacilli may be retained *in toto*, or eliminated in large part according to the conditions of *in vitro* cultivation.

SUMMARY

Bovine tubercle bacilli cultivated through as few as three generations at different pH values exhibit differences in virulence. These differences in virulence are associated with differences in colony form. Cultivation at pH 6.0 yields a maximum of R colonies and causes marked attenuation. Cultivation at pH 6.4 yields first S and later R colonies, the former being virulent and the latter considerably attenuated. Cultivation at pH 6.8 yields a maximum number of smooth colonies and this proves to be the optimum pH for preservation of virulence. Cultivation at pH 7.2 yields flat, granular colonies which are slightly attenuated but not markedly so.

None of the colonial variants derived from an avirulent strain exhibit pathogenic properties of note.

The weights of the lungs and the spleen are good indices of the extent of lesions in uncomplicated experimental tuberculosis.

Intracerebral inoculation of carefully selected guinea pigs is an excellent method for the biological titration of virulence of tubercle bacilli.

Some sources of apparent discrepancy in the recent literature on dissociation of tubercle bacilli are discussed.

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HISTOPATHOLOGY OF EXPERIMENTAL TUBERCULOSIS[1,2]

The Lesions Induced by Bovine Tubercle Bacilli of Varying Degrees of Virulence

KENNETH C. SMITHBURN

In the preceding paper (1) it was shown that tubercle bacilli of a single strain grown on media adjusted to different pH values exhibit striking differences in virulence. These differences were demonstrated by variations in survival time of animals inoculated with the various lines of cultures, and by the extent of lesions produced by them. It is the purpose of the present communication to set forth the pathological picture of lesions induced by attenuated microörganisms, and to compare them with lesions produced by microörganisms of greater virulence.

In 1933 Medlar and Sasano (2) demonstrated striking differences in the histopathology of lesions produced by attenuated BCG and by BCG which became virulent after cultivation on a special medium. They stressed the rôle of the polymorphonuclear neutrophile in the lesions induced by the virulent microörganisms. About the same time Winn and Petroff (3) reported their studies on the dissociation of avian tubercle bacilli and discussed the pathological picture of the disease induced by four variants of different virulence. They emphasized the increase of polymorphonuclear leucocytes (eosinophiles) in the blood of chickens inoculated with the virulent colonial variants (S) and the formation of abscesses in the corresponding lesions. The tubercles induced by attenuated (R) variants were small, circumscribed, surrounded by lymphocytes, and showed no abscess formation. Steenken, Oatway and Petroff (4) also demonstrated differences in the pathology of lesions induced by virulent and attenuated variants of human tubercle bacilli (H37).

The experiments reported in the previous paper (1) gave abundant material for the study of the lesions produced by four variants derived

[1] Presented in part at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

[2] From the Laboratories of The Rockefeller Institute for Medical Research, New York City.

from a single strain of bovine tubercle bacilli, each possessed of different properties of virulence.

EXPERIMENTAL

The material used in this study was obtained in the three experiments reported in the previous paper (1). It consisted of microscopical sections of tissues from seventy-four rabbits inoculated intravenously, and from thirty-nine guinea pigs inoculated intracerebrally. Sixteen of the rabbits were inoculated in groups of four each with cultures of the avirulent strain, Bovine 32, grown through three generations on Corper's medium adjusted to pH 6.0, 6.4, 6.8 and 7.2. Sixteen other rabbits were inoculated in groups of four with similar cultures of the virulent strain, Bovine 39, grown through three generations at pH 6.0, 6.4, 6.8 and 7.2. The remaining forty-two rabbits were inoculated with cultures of the bovine strain 39, fifth generation, grown at pH 6.0, 6.4, 6.8 and 7.2. Ten animals received 0.01 mgm. of one of the four cultures, while two individuals received a tenfold dose (0.1 mgm.) of the culture grown at pH 6.0. Of the thirty-nine guinea pigs which succumbed in the third experiment (1), twelve received microörganisms grown at pH 6.8, and a similar number received microörganisms grown at pH 7.2. Of these groups of twelve, four received a dose of 0.01 mgm., four received 0.000,1 mgm., and four received 0.000,001 mgm. Ten animals received microorganisms grown at pH 6.4; three were inoculated with 0.01 mgm., four with 0.000,1 mgm., and three with 0.000,001 mgm. Finally, five of the thirty-nine animals received microörganisms grown at pH 6.0; three were inoculated with 0.01 mgm. and two with 0.000,1 mgm. These thirty-nine animals represent all those which succumbed out of a group of forty-eight inoculated. The cultures used for the inoculation of these animals were of the seventh generation grown at the pH values indicated.

Tissues of the animals were fixed in Helly's fluid, except brains, which were fixed in 10 per cent formalin. Sections were prepared and, as routine, were stained with haematoxylin and eosin. From the rabbits, sections of lung, spleen, and bone marrow were stained with anilin-fuchsin, haematoxylin and light green F.S. (Grübler) to demonstrate tubercle bacilli. From the guinea pigs similar sections of brain, lung, and spleen were prepared.

OBSERVATIONS

None of the animals inoculated with cultures of the avirulent bovine strain 32 showed more than a very few tuberculous lesions. These were

invariably microscopical and of the type which will be described as "chronic" in the following paragraphs. Bacilli of this strain grown at one pH value induced lesions precisely like those induced by microörganisms grown at the other pH values.

In the previous report (1) very marked differences were demonstrated in the survival time and in extent of lesions in animals inoculated with virulent as compared with those receiving attenuated cultures of the bovine strain 39. Equally striking differences were noted in the character of the lesions. The extremes of the lesions, that is, those produced by the most virulent (grown at pH 6.8) and the most attenuated (grown at pH 6.0) microörganisms will be discussed first. Later the lesions produced by cultures of intermediate virulence (grown at pH 7.2 and pH 6.4) will be described.

The lesions in animals inoculated with the most attenuated cultures (grown at pH 6.0) were usually circumscribed, approximately round, and for the most part small, though in some animals killed 6 months after inoculation they were larger and confluent. They showed little tendency to perforate bronchi, and no affinity for blood vessels. Figure 1 shows chronic, circumscribed, noninvasive lesions in the lung of a rabbit inoculated with a culture attenuated by cultivation at pH 6.0. Histological structures included in the lesions (such as renal glomeruli or tubules) often appeared quite normal. The margins of lesions were usually sharp, giving the appearance that defensive forces were adequate to control the process. Figure 2 shows a circumscribed tubercle in the kidney, produced by an attenuated microörganism. This section is from the same animal as figure 1. The lesions were almost invariably organized and simple as regards their cellular components. The predominating cell was, of course, the modified monocyte or epithelioid cell. But lymphocytes were numerous in the lesions and especially at their periphery. Figures 3, 4 and 5 show lesions produced by attenuated microörganisms in lung (figure 3), liver (figure 4), and brain (figure 5). Note the abundance of lymphocytes in these lesions. Caseation was minimal and there were, as a rule, few or no polymorphonuclear leucocytes in these lesions. Often, but not invariably, there was a considerable band of fibrous connective tissue at the periphery of the lesion. Very old lesions, especially in spleen or bone marrow, were occasionally composed of small clumps of epithelioid cells, with no other cells present. Giant cells were sometimes, but not invariably, present. Lesions in heart, intestine and adrenals were never seen after inoculation with attenuated microörganisms

grown at pH 6.0, and in the kidneys, liver and bone marrow they were uncommon.

Tubercle bacilli were never numerous in this type of lesion. Often no bacilli could be found in any of the lesions, and when present their number was small. Occasional small clumps of the bacteria were found in tiny caseous foci.

That lesions were also less numerous and less extensive in animals inoculated with the attenuated cultures may be seen by comparing figures 1 and 6. The latter is a section of lung from an animal receiving

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PLATE 1

FIG. 1. Lung of rabbit R 3793, sacrificed 40 days after intravenous inoculation with 0.01 mgm. of the third cultural generation of bovine strain 39 grown at pH 6.0 (markedly attenuated). Lesions are small, circumscribed and surrounded by lymphocytes. H. & E., × 11.5.

FIG. 2. Kidney of same rabbit as lung in fig. 1. Note circumscribed character of the lesion and dark ring of cells at periphery. H. & E., × 25.

FIG. 3. Tubercle in lung of rabbit R 4362, sacrificed 162 days after intravenous inoculation with 0.1 mgm. of fifth cultural generation of bovine strain 39 grown at pH 6.0 (markedly attenuated). Lesion is circumscribed and composed simply of epithelioid cells with a border of lymphocytes. H. & E., × 150.

FIG. 4. Circumscribed tubercle in the liver of rabbit R 4353, sacrificed 161 days following intravenous inoculation of 0.01 mgm. of fifth cultural generation of bovine strain 39 grown at pH 6.0. This lesion was the only one in the section. H. & E., × 150.

FIG. 5. A chronic, circumscribed tubercle in the olfactory area of the brain of guinea pig R 4954. The animal died 43 days following intracerebral inoculation of 0.01 mgm. of seventh cultural generation of bovine strain 39 grown at pH 6.0 (markedly attenuated). This and one similar lesion were the only ones in the block. Note heavy infiltration with lymphocytes and absence of necrosis. H. & E., × 150.

FIG. 6. Acute, invasive lesions in the lung of rabbit R 3797, sacrificed 41 days after inoculation with 0.01 mgm. of third cultural generation of bovine strain 39 grown at pH 6.8 (virulent). Note irregular shape of lesions, invasion and perforation of bronchioles, and extensive caseous necrosis. Compare with fig. 1. H. & E., × 11.5.

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virulent bovine strain 39 (grown at pH 6.8) and shows large, caseous lesions of irregular shape, some of them perforating bronchioles. Figures 5 and 7 illustrate the character and extent of lesions produced in the brain and meninges by attenuated and by virulent microörganisms. Figure 5 shows one "chronic" tubercle in the brain of a guinea pig inoculated with bovine strain 39 grown at pH 6.0. One other such lesion was present and these two constituted the only lesions in the section. Figure 7 shows a section from the brain of an animal receiving bovine strain 39, the virulence of which was maintained by cultivation at pH

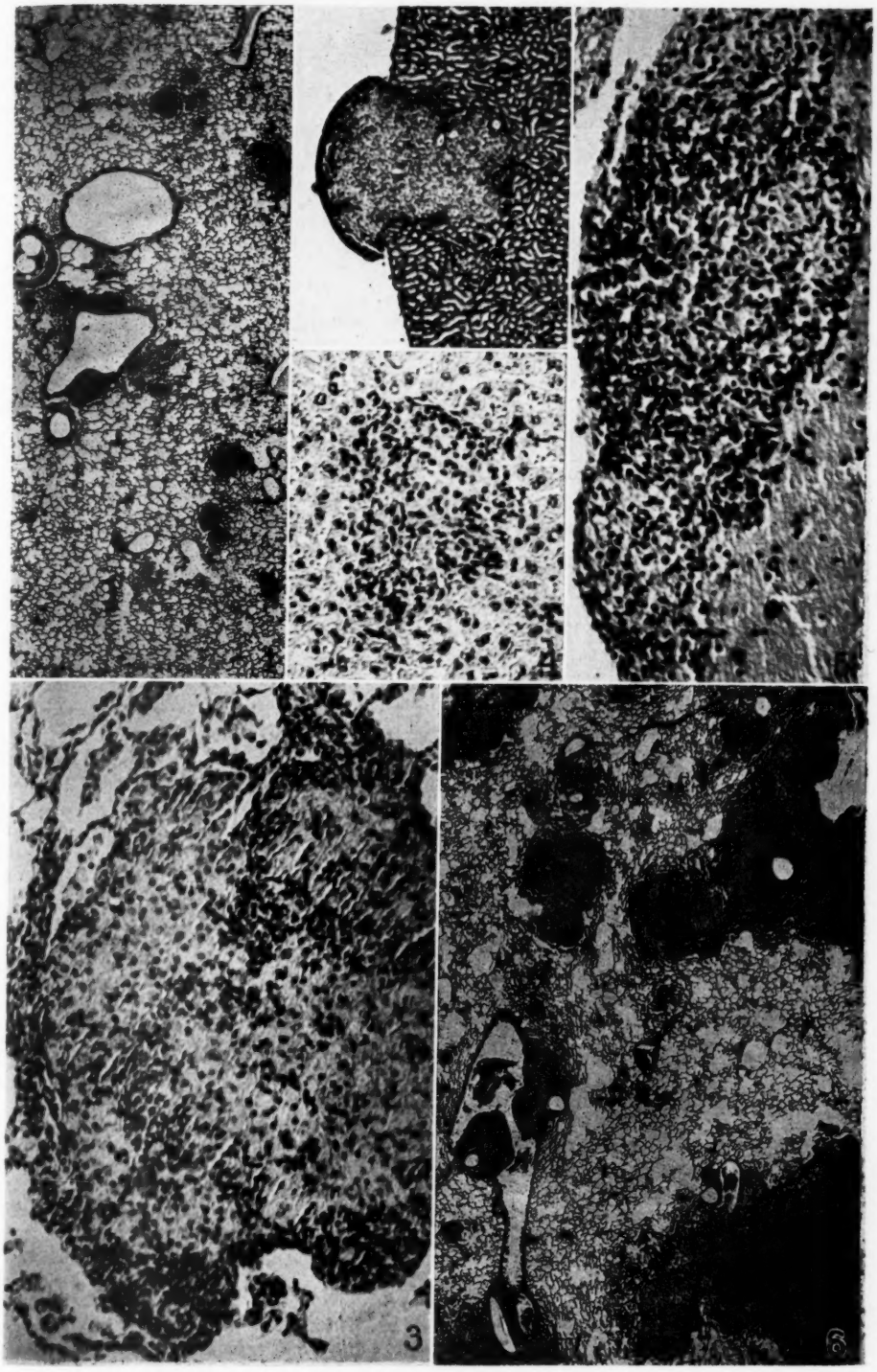

PLATE 1

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6.8. The entire base of the brain, part of the vertex, and the entire cerebellum were covered with an exudate such as is shown, and there were numerous parenchymatous foci as well.

In view of the benign appearance of lesions induced by attenuated variants, and the small number of lesions produced even by large doses, it seems probable that these microörganisms cause death after intracere-

PLATE 2

FIG. 7. Acute, invasive lesions in the meninges and brain of guinea pig R 4946 which died 38 days after intracerebral inoculation with 0.000,001 mgm. of the seventh cultural generation of bovine strain 39 grown at pH 6.8 (virulent). Note perivascular infiltration of cortical blood vessels and tiny foci of neutrophiles and of necrosis. These lesions contained innumerable acid-fast bacilli. The dose in this animal was one ten-thousandth that given to the animal, the brain of which is shown in fig. 5. H. & E., × 150.

FIG. 8. Spreading, invasive lesion in the kidney of rabbit R 3794, sacrificed 40 days following intravenous inoculation with 0.01 mgm. of third cultural generation of bovine strain 39 grown at pH 6.4. The indefinite border of the lesion and extensive caseous necrosis are characteristic of the acute lesions. At higher magnification the lesion could be seen to be very complex in cellular structure. Compare with fig. 2. H. & E., × 25.

FIG. 9. Acute, tuberculous lesion in the myocardium of rabbit R 4282 which died 50 days following intravenous inoculation with 0.01 mgm. of fifth cultural generation of bovine strain 39 grown at pH 6.8 (virulent). Note caseous necrosis at centre and diffuse, spreading periphery. The lesion contained many tubercle bacilli. H. & E., × 150.

FIG. 10. Tuberculous lesion in the lumen of a vein in the lung of rabbit R 4351. Animal died 47 days following intravenous inoculation with 0.01 mgm. of fifth cultural generation of bovine strain 39 grown at pH 6.8. Note detached clump of epithelioid cells indicating haematogenous spread. Acid-fast stain showed epithelioid cells containing tubercle bacilli exposed to the circulating blood. Serial sections revealed that the vein was practically occluded at one point and also showed that the lesion perforated the wall of the vein. However, it could not be determined whether the lesion had arisen within or without the vein. H. & E., × 150.

FIG. 11. An acute lesion with extensive necrosis perforating a vein in the lung of rabbit R 4364. Animal died 85 days following intravenous inoculation of 0.01 mgm. of fifth generation culture of bovine strain 39 grown at pH 7.2. In this case the lesion obviously had origin outside the vessel. Acid-fast stain showed cells containing tubercle bacilli exposed to the circulating blood. The extensive necrosis and invasion of neutrophiles are charateristic of the acute lesions. Haematoxylin, anilin-fuchsin and light green. × 115.

bral inoculation only when lesions happen to be located in some vital centre of the nervous system. Some of the deaths in animals inoculated with the attenuated variants were due to intercurrent infections (reference 1, table 7), but others could not be explained on this basis. And since the lesions were minimal in extent, it seems probable that the fatal issue may have been determined by the location of one or more lesions. However, survival time was invariably much longer in these animals than

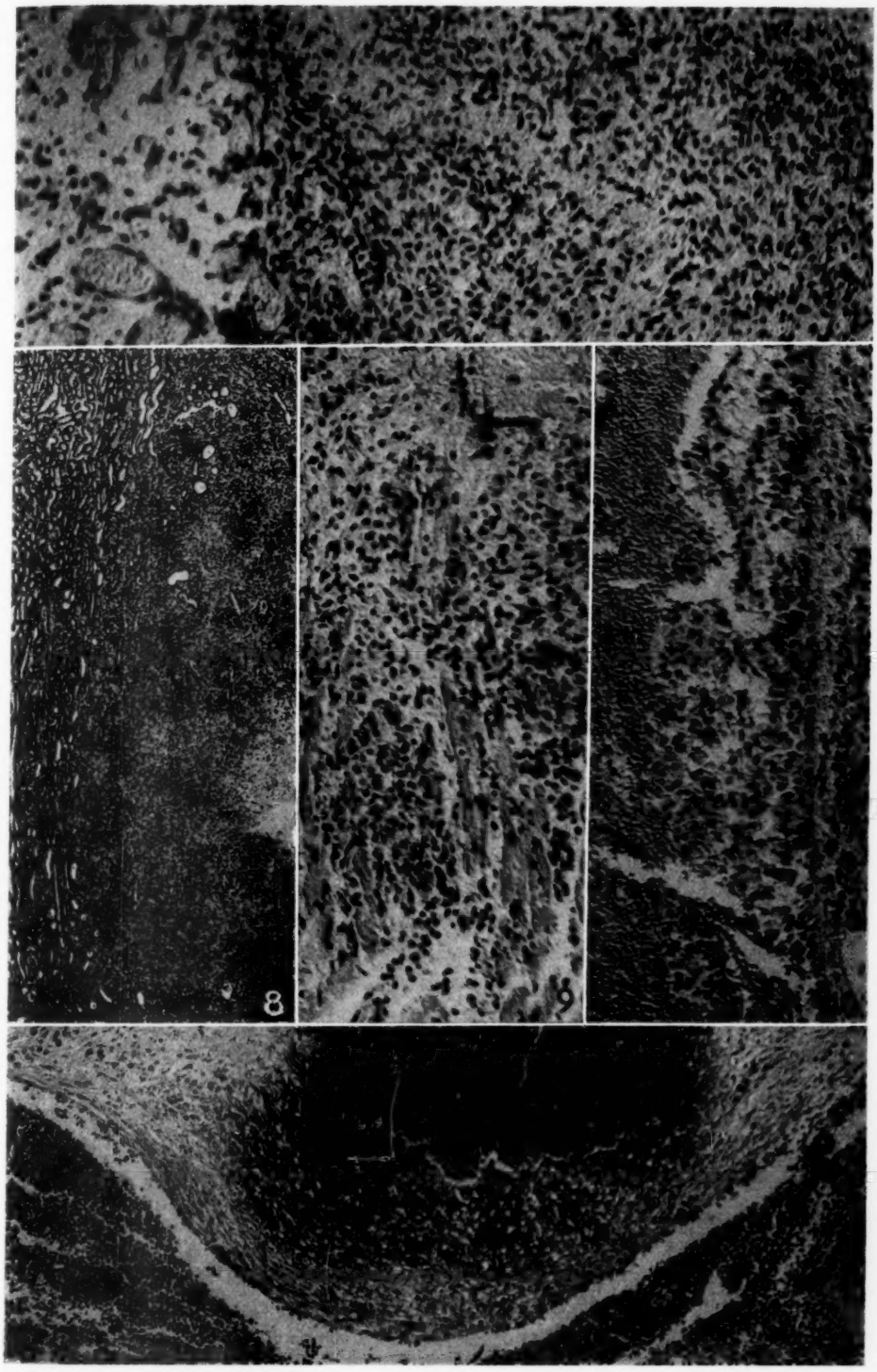

PLATE 2

in animals receiving even the smallest dose of the most virulent microorganisms.

The lesions produced by virulent variants, the pathogenicity of which was maintained by cultivation at pH 6.8, presented a wholly different picture. They were massive in extent in lung, spleen, liver, kidney, bone marrow and lymph nodes; and lesions in the heart, intestine and adrenal were frequently seen. Wherever seen the lesions were usually large, apparently unconfined, and highly invasive. Figure 6, taken at low magnification, shows the invasive character of the lesions; they may be seen to perforate a bronchiole. Figure 7 likewise shows the invasive character of lesions which were extending from meninges to brain directly and by perivascular infiltration. Figure 8 shows an invasive lesion in the kidney of an animal inoculated with virulent bovine strain 39, third generation grown at pH 6.4. The magnification is the same as in figure 2, but in figure 8 the lesion may be seen to be spreading into the adjacent kidney structures. Figure 9, showing a section from the heart of an animal inoculated with the virulent organisms, demonstrates the invasive character of the lesions which are extending between the muscle bundles and destroying the latter as they progress. Figure 10 shows a lesion within the lumen of a vein and a small group of detached cells free in the circulating blood.

The lesions produced by the virulent microörganisms were extremely complex in their structure. Little evidence of organization existed and every variety of connective tissue cell was present. Epithelioid cells were most numerous, but there were many monocytes, polymorphonuclear leucocytes, plasma cells, fibroblasts and macrophages. The lymphoid reaction was usually minimal and lesions were not surrounded by a ring of lymphocytes and connective tissue. Necrosis and caseation were extensive. Relatively few giant cells were seen. Lesions in brain and meninges, produced by intracerebral inoculation of bovine strain 39 grown at pH 6.8, usually showed very numerous polymorphonuclears.

Parenchymatous structures, such as renal glomeruli or tubules, or heart muscle, which were included in these acute lesions or adjacent to them, often showed marked degenerative change, suggesting the possibility of the elaboration of a cytotoxic substance by the microörganisms.

Lesions involving the bronchi and blood vessels were numerous in the lungs of animals inoculated with the most virulent bacilli. One could not be certain whether a lesion such as that in figure 10 had taken origin inside or outside the vessel. But a tubercle which obviously took origin

without the vessel and which was encroaching on the lumen is shown in figure 11. Bacterial stains of this section showed innumerable tubercle bacilli, some of which were in cells exposed to the circulating blood. This indicated that spread of the lesions took place in three ways, namely, direct extension, by way of the bronchi, and by way of the blood.

The lesions produced by the most virulent microörganisms invariably showed far greater numbers of acid-fast bacilli than those produced by attenuated microörganisms. Often the bacilli were extremely numerous. Figure 12 shows a section of spleen stained with anilin-fuchsin and exhibiting many tubercle bacilli. This animal was inoculated with the virulent microörganisms grown at pH 6.8.

In the previous paper (1) it was shown that cultivation of the bovine strain 39 at pH 7.2 caused slight attenuation, while the same bacilli cultivated through five to seven generations at pH 6.4 became even more markedly attenuated. Careful histological studies were therefore made to determine whether still different varieties of lesions were produced in animals inoculated with these microörganisms. These studies showed that the microörganisms grown at pH 7.2 and showing only slight attenuation produced, for the most part, lesions closely resembling those seen after inoculation of the more virulent microörganisms. The lesions were usually large, irregular in contour, invasive and of complex cellular composition. Typical acute, spreading lesions in the lung of such an animal are shown in figure 13 (to be compared with figures 1, 3 & 6), and characteristic lesions induced by the same microörganisms in the brain are shown in figure 14 (to be compared with figures 5 and 7). Very occasional lesions of moderate size with good lymphoid reaction, no polymorphonuclear leucocytes and no caseation were seen, undoubtedly due to attenuated elements inoculated, but the "acute" type of lesions predominated. As with the more virulent microörganisms, there was rather frequent involvement of the heart, intestines and adrenals. Tubercle bacilli were numerous, although slightly less so than in animals inoculated with the more virulent microörganisms grown at pH 6.8. Caseation was extensive, as a rule, regardless of where the lesions were situated, and bronchial or vascular invasions were frequently seen. The large tubercle invading a pulmonary vein in figure 11 was present in an animal inoculated with the culture grown at pH 7.2.

The lesions produced by microörganisms grown at pH 6.4 were also of mixed type. However, the chronic type of lesion was more frequently seen than in any other animals save those inoculated with the most

attenuated culture (grown at pH 6.0). Figure 15 shows a chronic tubercle and figure 16 shows an acute, spreading lesion, both in the lung of one animal which was killed 162 days after inoculation. Figure 15 closely resembles figure 3, while the lesion in figure 16 is similar in type to those in figures 10 and 13. Invasion of bronchi and veins was seen less frequently than after inoculation of the more virulent microörganisms but did occur. Moreover, lesions involving the adrenals or the

PLATE 3

FIG. 12. Necrotic centre of an acute lesion in the spleen of rabbit R 4352. Animal received same inoculum and died on same day as rabbit R 4351, a lesion from which is shown in fig. 10. Note very large numbers of tubercle bacilli in the caseous material. Haematoxylin, anilin-fuchsin and light green. × 1000.

FIG. 13. Tuberculous lesion in lung of rabbit R 4291 which was killed when moribund, 122 days after intravenous inoculation of 0.01 mgm. of fifth cultural generation of bovine strain 39 grown at pH 7.2. Photograph shows the periphery of a large lesion with irregularly advancing edge. Note absence of lymphocytes. H. & E., × 150.

FIG. 14. Acute, tuberculous lesions in meninges and cerebral cortex of guinea pig R 4952 which died 39 days following intracerebral inoculation with 0.000,1 mgm. of seventh cultural generation of bovine strain 39 grown at pH 7.2. Note necrosis and infiltration of neutrophiles, extension into cortex along perivascular sheaths, and absence of a limiting border of lymphocytes. H. & E., × 150.

FIG. 15. Circumscribed tubercle in the lung of rabbit R 4366, killed 162 days after intravenous inoculation of 0.01 mgm. of fifth cultural generation of bovine strain 39 grown at pH 6.4. Compare with fig. 3. Both illustrate simple cellular composition of the "chronic" tubercle and each has a pronounced border of lymphocytes. H. & E., × 150.

FIG. 16. Acute, spreading lesion in same section as the lesion shown in fig. 15. Note irregular peripheral spread of the process, and the lack of lymphocytes at the border. This illustrates that both acute and chronic lesions occur long after the original inoculation, provided the microörganisms inoculated include both virulent and attenuated elements. H. & E., × 150.

FIG. 17. An acute, spreading and a chronic circumscribed lesion in the meninges of a guinea pig, R 4956, which died 39 days following intracerebral inoculation of 0.000,1 mgm. of the seventh cultural generation of bovine strain 39 grown at pH 6.4. The chronic lesion is very heavily infiltrated with lymphocytes and no tubercle bacilli could be found in it. The acute lesion shows minimal lymphoid reaction. Numerous neutrophiles and tiny foci of necrosis; acid-fast stains showed many tubercle bacilli. H. & E., × 150.

intestine were occasionally present, although lesions in the heart did not occur. The large, irregular lesions were usually extensively caseous and complex in cellular composition, while the circumscribed lesions were composed almost wholly of epithelioid cells and lymphocytes. Tubercle bacilli were numerous in the "acute" and scarce in the "chronic" type of lesion. Although some of the "acute" lesions showed rather marked lymphocytic infiltration (perhaps produced by both attenuated and

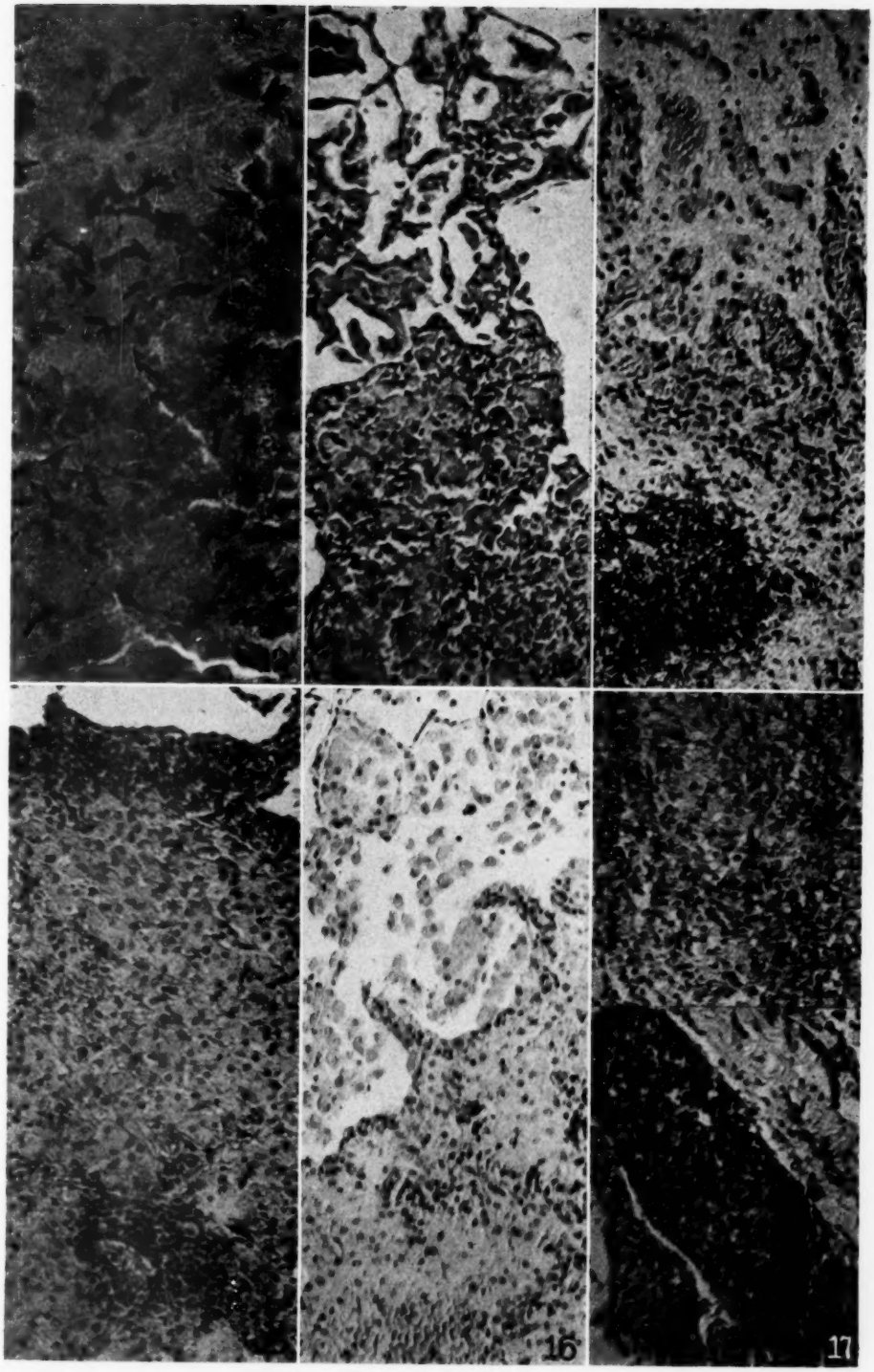

PLATE 3

virulent bacilli), no special types of lesions were found. Figure 17, a section from the brain of a guinea pig inoculated with microörganisms grown at pH 6.4, shows an acute and a chronic type tubercle which were in adjacent fields of the same section. Note the massive lymphocytic infiltration of the one lesion and the lack of lymphocytes in the other.

DISCUSSION

By the simple expedient of cultivating a single strain of virulent tubercle bacilli through successive generations on culture medium adjusted to different pH values, it was found not only that the colony morphology was markedly influenced (5) but the virulence of the microörganisms also underwent significant change (1). The studies reported here further show that changes in virulence were associated with changes in the histogenesis of lesions. Cultivation of the bovine strain 39 at pH 6.0 yielded a maximum of coarsely granular (R) colonies (5) which were shown to be markedly attenuated (1). The present report shows that the lesions produced by such microörganisms were remarkably different in appearance from the lesions produced by more virulent microörganisms. We are inclined to believe, like Medlar (2), that these classical, hard tubercles are largely regressive or self-limited.

Cultivation of the same microörganism through successive generations at pH 6.8 yielded a maximum number of smooth colonies (5) which were fully virulent (1). The lesions produced by these microörganisms were highly invasive, acute and very prone to caseation.

By contrast with the above, the same microörganisms grown in successive generations at pH 7.2 produced colonies which we have called intermediate (5) and which were only slightly attenuated (1). The lesions induced by inoculation of these microörganisms were principally of the acute type, but some lesions of the chronic type occurred.

Cultivation of the same bovine strain 39 through successive generations at pH 6.4 yielded at first smooth colonies (5) which were virulent (1) and later granular colonies which were attenuated (1). The lesions produced by these attenuated microörganisms were in part of the acute, and in part of the chronic type.

These results lead us to believe that the slightly attenuated microorganisms grown at pH 7.2 and the more attenuated bacteria grown at pH 6.4 were mixtures of the most virulent (S) and the most attenuated (R) microörganisms, that the "intermediate" colonies grown at pH 7.2 consisted chiefly of S elements with but a few attenuated forms, while

the more granular colonies grown at pH 6.4 were composed of a smaller percentage of S and a greater percentage of R colonies.

That the results obtained in this study are not due to the diphasic nature of experimental tuberculosis demonstrated by Thomas (6) is evident from the fact that animals receiving the most attenuated microorganisms and killed within 30 or 40 days showed chronic type lesions (figures 1, 2 & 5). Moreover, animals receiving more virulent microorganisms and surviving beyond the first phase of the disease still showed the acute type of lesions (figures 13 and 16). For examples of this fact see figure 13, an acute lesion in the lung of an animal which was sacrificed when moribund 122 days after inoculation, and figure 16, from an animal sacrificed 162 days after inoculation. Moreover, the occurrence of acute and chronic lesions in the same animal at the same time (figures 15, 16 & 17) points rather to the influence of bacteria of different potentialities than to the fact that the disease was of diphasic character. That experimental tuberculosis induced in unselected animals by undissociated tubercle bacilli is of a diphasic nature is not to be denied. Under such circumstances resistant animals (receiving perhaps a few less virulent microörganisms) survive into the second phase, whereas highly susceptible animals (some perhaps receiving a maximum of virulent elements) succumb during the first phase. However, in the present experiments every effort was extended to eliminate factors of individual resistance so that we believe the results obtained were largely or wholly due to the properties of the bacteria.

Our results indicate that, as Medlar (2) has already shown, the acute reaction in the lesions produced by the most virulent microörganisms is due to properties associated with the bacteria rather than to allergy as believed by Rich and McCordock (7). We have observed "acute" lesions in guinea pigs inoculated intracerebrally and dying without becoming demonstrably hypersensitive to tuberculin. Moreover, tuberculous guinea pigs are known to be considerably more allergic to tuberculin than rabbits, yet the exudative reaction in each is approximately equal. Finally, the occurrence of both acute and chronic lesions in the same animal at the same time, following inoculation with cultures composed of both virulent and attenuated microörganisms, strongly suggests that allergy is not responsible for the histogenesis of the acute lesions. Were this the case, every lesion in a given individual should be of the same type, the latter depending on the allergic state at the moment.

SUMMARY

A histological study was made of tuberculous lesions induced by bovine tubercle bacilli cultivated at various pH values and previously shown to differ markedly in virulence. The cultures which were most virulent produced invasive lesions with marked tendency to necrosis. The cultures which were most attenuated induced circumscribed, noninvasive tubercles of simple structure. Microörganisms which were intermediate in virulence induced the formation of both types of lesions, the relative proportion of each depending on the virulence of the microörganism. The result indicates that colonies intermediate in morphology and virulence between R and S are not distinct types but are mixtures of these elements.

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HAEMATOLOGICAL STUDIES IN EXPERIMENTAL TUBERCULOSIS[1,2]

Variations in the Blood Cells of Rabbits Inoculated with Cultures Differing in Virulence

K. C. SMITHBURN, F. R. SABIN AND L. E. HUMMEL

As long ago as 1896, it was observed that there were changes in the cells of the circulating blood during tuberculous infection. Holmes (1) stated that the characteristic changes were: a decrease in small lymphocytes, an increase in phagocytes (neutrophiles), usually an increase in large lymphocytes (probably monocytes, as these cells were not then differentiated from lymphocytes), a decrease or disappearance of the eosinophiles, and certain qualitative changes of disintegrative nature involving in particular the phagocytes. Subsequent work has elucidated and elaborated upon Holmes's work, but the basic observations still stand. Arneth (2) and Lewis (3) observed qualitative and quantitative changes in the neutrophilic leucocytes, which were believed by Arneth (2) to be specific and diagnostic for tuberculosis. The latter was shown not to be the case by Lewis (3). In 1902 Lacapère (4) noticed changes in the blood cells very soon after inoculation of tubercle bacilli. The most constant change was an increase in the number of large mononuclear cells. Webb and his associates (5 to 8) later found that lymphocytosis was associated with increased resistance and that lymphopenia was evidence of advancing disease. Webb (8) believed that lymphocytes were able to engulf tubercle bacilli. But the identification of the monocyte by Schilling (9) and by Sabin (10), and subsequent studies of their phagocytic properties by Sabin and Doan (11), Lurie (12), Gottlieb (13) and others have shown that it is this cell and not the lymphocyte which has the capacity to engulf tubercle bacilli. However, the work of Webb on the relation of lymphocytes to resistance in tuberculosis was confirmed and extended by Murphy and his coworkers (14 to 18). It has also been indicated (39, 43) that the state of maturity of the lymphocyte

[1] Presented in part at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

[2] From the Laboratories of The Rockefeller Institute for Medical Research, New York City.

may be important; induced lymphocytosis does not invariably result in enhanced resistance (39).

The identification of the monocyte (9, 10) made possible studies of the rôle of this cell in tuberculosis. Cunningham, Sabin, Sugiyama and Kindwall (19) observed that with advancing disease the monocytes increase in number, while the lymphocytes decrease, so that there is an elevation of the monocyte-lymphocyte ratio. Studies by Sabin, Doan and Cunningham (20) further emphasized the significance of the monocyte-lymphocyte ratio. These experimental studies have received ample confirmation in both the laboratory and clinic (21 to 26, 35).

Recently Medlar (27, 28) has studied the blood cells in clinical tuberculosis; he has stressed the rôle of the neutrophilic granulocytes and discussed the relation between the blood picture and the evolution of lesions in the tissues. The part played by each of the blood cells was discussed and three types of leucocytic patterns were observed in his patients. These were described as the septic, hyperplastic and nonseptic types (28). Crawford (29) devised a simple calculator for determining the leucocytic index, which takes into account the neutrophile-lymphocyte ratio and abnormal values for monocytes and total white cell count. This index was used by Medlar in extensive clinical studies (30 to 32). Sweany (26) has employed both the lymphocyte-monocyte and the neutrophile-lymphocyte ratios, together with erythrocyte sedimentation and certain chemical findings, and has devised charts which express graphically the course of events.

As result of these earlier studies, it is generally agreed that carefully performed total and differential leucocyte counts are of considerable prognostic value in experimental and clinical tuberculosis. It is believed that the results to be described in the following paragraphs throw new light on the rôle of the various blood cells in reflecting the course of tuberculous infection.

MATERIALS AND METHODS

The animals used in this study and the experimental procedures, except blood counts, were described in the first paper (36) and will be repeated here only briefly.

Forty normal, young adult, New Zealand red rabbits were used. Studies of the blood were made in the period from September to December, 1935. The animals were then divided into four groups of ten each with litter mates equally distributed. Animals of different age, sex

and weight were so distributed as to make the four groups as nearly alike as possible.

Four lines of cultures, each derived from the bovine strain 39, and grown for five successive generations at pH values of 6.0, 6.4, 6.8 and 7.2, were used. Differences in pathogenic properties of these bacteria were known to exist, as determined from results of a prior experiment. Each of the cultures was inoculated intravenously into one group of ten rabbits. A standard dose of 0.01 mgm. (moist weight, about 500,000 bacteria) was used throughout. Before and after inoculation, all animals were kept under similar conditions. None was subjected to any therapeutic procedure.

Following inoculation, counts of the blood cells were done on each rabbit once weekly until death from tuberculosis occurred, or until the last remaining animals were sacrificed 6 months following inoculation. Haemoglobin determinations were done by the Newcomer method; all were read by one disinterested person to whom the identity of the individual animals was unknown. Standardized blood diluting pipettes and standardized double-ruled Levy-Hauser counting chambers were employed for the blood counts. Differential leucocyte counts were done by the authors, using the supravital technique; identity of the rabbits was unknown to the individuals making the counts. As routine, 100 cells were counted on each of two coverslip preparations; when there were appreciable differences between the two counts, as many as 1,000 cells were counted. Total erythrocyte and leucocyte counts were done by competent technicians experienced in this work.

Statistical analyses of the blood studies were made following the termination of the experiment. Data for each group of ten animals were treated separately. The 75 counts done on each group prior to inoculation served as specific controls. Counts following inoculation were analyzed by months, that is, all the counts on one group during the first month after inoculation were treated together, etc. Values for the absolute number of each of the blood cells were used. Employing the methods and formulae outlined by Davenport and Ekas (33), the mean, standard deviation and probable error of the mean were determined for each type of blood cell in each group of animals for each time interval, namely, control period, first month after inoculation, second month, etc. The significance of changes in the various blood cells was determined by calculating the deviation from the control mean, determining the probable error of this deviation, and dividing the former by the latter.

This quotient expresses the deviation as a multiple of its probable error. The statistical significance (probability) of various values of such quotients was taken from Pearl's (34) table 40. From this table (or Davenport and Ekas's (33) table 11, p. 178), it may be seen that deviations having the value of PE $\times$ 3.8 occur by chance only once in 96 times, and those having the value PE $\times$ 3.9 occur by chance only once in 117 times. Therefore the value PE $\times$ 3.85 was taken as the limit for normal variation; and deviations of order greater than this have a probability of 100 to 1, or more, of being significant. Deviations of lesser order were considered not to be of certain significance. The shaded areas on charts 1 to 5 show the magnitude only beyond which deviations of the mean counts were considered to be certainly significant. Comparisons of the deviations in any one type of cell in one group of rabbits with those in a group inoculated with a different culture were thus made, not on the basis of a common normal value, but on the basis of the normal value obtained in each particular group. It should be mentioned, however, that differences in the mean normal values among the four groups were not of high order.

The monocyte-lymphocyte ratios, proposed by Cunningham, Sabin, Sugiyama and Kindwall (19), and the neutrophile-lymphocyte ratios, proposed by Crawford (29), were calculated for each individual count; these data were thereafter treated in precisely the same manner as those for the blood cells.

The data included 300 counts done before inoculation and 609 counts done after inoculation. The grouping of data during the disease period was such that the mean values represented not less than seven and not more than forty-five counts.

RESULTS

The marked differences in virulence of the four cultures used for inoculation of the four groups of animals (36) made possible a study of the blood cells in various grades of tuberculous infection from mild to severe. It was shown (36) that the culture grown at pH 6.0 was markedly attenuated (virulence +), that grown at pH 6.4 was moderately attenuated (virulence ++), that grown at pH 7.2 was slightly attenuated (virulence +++), and that grown at pH 6.8 was fully virulent (++++). Hereafter, in order to facilitate discussion, the four groups of animals will be referred to by numbers 1 to 4, corresponding to the virulence of

the culture, group 1 being that inoculated with the least virulent culture, etc. Among the four groups of animals, each type of blood cell at some time in the disease showed significant change from the normal. In presenting the data, each type of cell and the two cellular ratios will be discussed separately. Finally, the efficiency of each cell in showing significant change will be discussed.

Haemoglobin: Each of the four groups of animals showed a significant fall in haemoglobin during the first month after inoculation, as shown on chart 1. The magnitude of this fall was greatest in those inoculated with the most virulent culture and least in those receiving the most attenuated culture. During the second month of the disease, only the animals of groups 3 and 4 showed significantly low values for haemoglobin. Paradoxically, however, the surviving animals of group 4 did not show abnormal values for haemoglobin during the third month. This may have been due to the fact that only seven counts were obtained and five of these were on the one animal of the group which survived more than 72 days. During the third and fourth months, only the animals of group 3 showed abnormally low haemoglobin. But in the fifth and sixth months, those of groups 1 and 2 also showed low values. Every significant deviation of haemoglobin from the normal was in the direction of a decrease. Of the nineteen means determined according to group per month, twelve were significantly low, giving an efficiency of 63.15 per cent.

Red blood cells: During the first month of the disease, only the rabbits of groups 4 and 2 showed marked decrease in the red blood cells, as shown on chart 1. During the second and third months, none of the groups showed abnormal values for red blood cells. In the fourth month, those of group 3 showed a decrease. In the fifth and sixth months, the rabbits of group 2 had red blood cell counts which were significantly low. The rabbits receiving the most attenuated culture (group 1) showed significantly low erythrocytes only in the sixth month. Roughly then, the anaemia was proportional to the severity of disease; but of nineteen mean values after inoculation only six were significantly low, giving an efficiency of only 31.57 per cent. All significant deviations were in the direction of a decrease, however.

Total leucocytes: In the first and second months following inoculation, only the animals of group 4, those inoculated with the most virulent bacteria, showed a significant change in total leucocyte count; this was a decrease. In the third month, none of the groups showed significant

deviation from the normal mean values. In the fourth month, groups 1 and 2 showed values which were abnormally high. Only group 2 exhibited an abnormal level for leucocytes in the fifth month, namely, a rise. In the sixth month, groups 1 and 2 showed significant elevation.

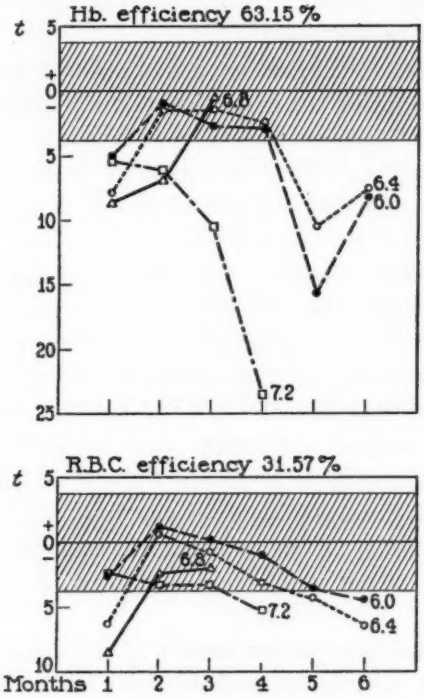

CHART 1.[3] Monthly mean deviations of haemoglobin and erythrocytes expressed as multiples of their probable error.

The decreases, recorded on chart 2, occurring in the animals inoculated with the more virulent organisms, exemplify the leucopenic phase described by Sabin, Doan and Cunningham (20). Of the nineteen mean

[3] Deviations in charts 1 to 5 inclusive are shown as multiples of the probable error of the deviations. The odds against occurrence by chance are small in the case of all points falling in the shaded zone and their significance is not certain. But the odds against occurrence by chance are high in the case of deviations falling outside the shaded zone; such deviations are considered significant. The horizontal line in the centre of the shaded zone represents the normal value; the direction of each deviation from the normal is shown. The whole number and decimal at the end of each curve indicate the pH of the medium on which the culture was grown for inoculation of the animals represented by that curve. The curves differ in length according to the survival time of the rabbits represented.

values in the four groups, seven deviated significantly from the normal, so that the efficiency was 36.84 per cent. Of these seven significant deviations, two were below the normal level and five were above. It was interesting that group 3, receiving the culture grown at pH 7.2 (virulence +++), at no time showed deviations of high order (chart 2).

Neutrophiles: Only the animals of group 4 showed abnormal values for neutrophiles in the first two months following inoculation. This change, a sharp decrease (chart 2), corresponded to the anaemia-leucopenia phase of the disease as demonstrated in table 1. In the third month

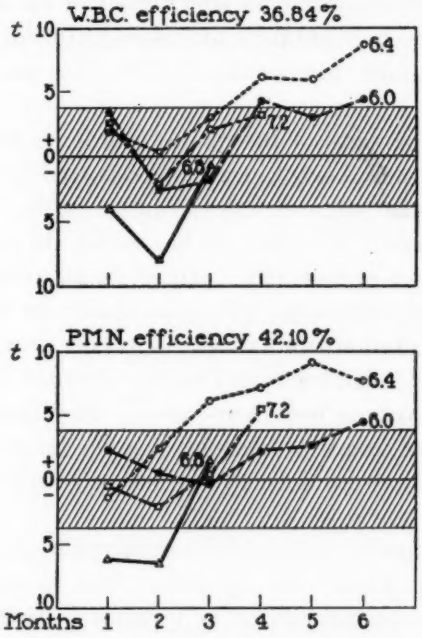

CHART 2. Monthly mean deviations of white blood cells and neutrophiles expressed as multiples of their probable error.

this group of animals exhibited normal values for neutrophiles, as did those of groups 3 and 1. However, the rabbits of group 2 showed an increase in neutrophiles at this time and thereafter the values were always significantly high in this group. In the fourth month the animals of group 3 showed an increase in neutrophiles. The group 1 which received the most attenuated culture exhibited only one abnormal monthly mean value, a rise in the sixth month. Of the nineteen mean values after inoculation in the four groups, eight showed significant deviation from the normal, giving an efficiency of 42.10 per cent. Two of these

eight significant deviations were in the direction of a decrease (in animals inoculated with highly virulent organisms) and six were in the opposite direction. It was interesting and probably important that the increases in neutrophiles which did occur, did not take place until the third month in any of the groups, despite the fact that the disease was sufficiently established in three of the four groups that deaths were occurring. Terminal neutrophilic leucocytoses were noted in certain individual animals but were not of sufficient magnitude to cause significant elevation of the mean for the groups. In the group receiving the most virulent microörganisms, in which most of the deaths occurred in 60 days or less, even individual counts taken just prior to death exhibited neutropoenia, although their lesions exhibited the most extensive caseation.

Basophiles: The counts of basophiles preceding inoculation in these groups of animals were lower than those reported by Pearce and Casey (37) and by Thomas (40). It was shown by Sabin, Miller, Smithburn, Thomas and Hummel (38) that the basophiles do not reach maximum levels until the time of maturity. Although all animals in the present experiment were of mature age when inoculated, at the midpoint of the period before inoculation twenty-four, or 60 per cent, were between 4.2 and 5.9 months old. Higher values might, therefore, have been obtained had the base-line counts been made later. However, the mean of the final preinoculation counts of basophiles in the forty animals was 631, a figure still below that obtained by the investigators mentioned; at this time each animal was at least 6 months old.

No significant change in basophiles occurred in the animals receiving the most virulent culture, at any time. But in the first month, the other three groups each exhibited an increase. In the rabbits of group 2 the rise extended through the second and third months. No other groups exhibited significant deviation in the second month. In the third month, those of group 3 again showed a significant rise, but in the fourth month there was a fall of equal magnitude. In the fourth, fifth and sixth months, the rabbits of group 1 again showed a rise in basophiles, while those of group 2 exhibited no significant deviation from the normal. Thus there were deviations of apparent significance in three of the four groups, some above and some below the normal. These changes were neither related to the virulence of the infecting agent, nor to the resistance of the host. Ten of the nineteen values following in-

oculation showed significant deviations from the normal. Of these, nine were in the direction of an increase, while one was in the opposite direction, as shown on chart 3. It is interesting to note that, during the leucopenic phase, the animals receiving the most virulent microörganisms did not exhibit a decrease in basophiles, although there was a decrease in all other cellular elements originating in the bone marrow. It is also notable that none of the apparently significant elevations of the basophile counts (see table 1) exceeded the normal values obtained by Pearce and Casey (37).

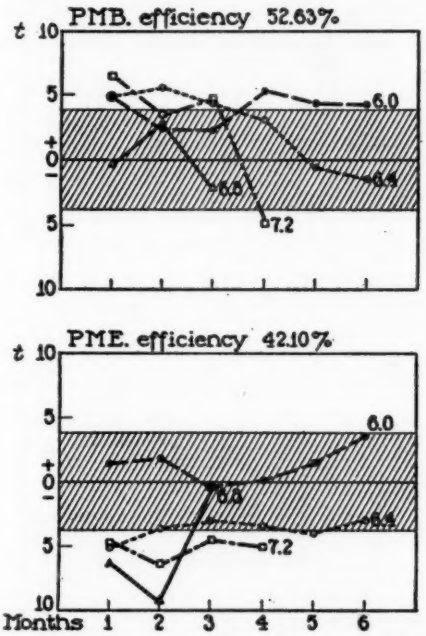

CHART 3. Monthly mean deviations of basophiles and eosinophiles expressed as multiples of their probable error.

Eosinophiles: Chart 3 shows that the ten animals of group 1 at no time showed significant deviations from the normal count of eosinophiles. Group 2 showed a significant decline in the first and fifth months only. Those of group 4 showed a significant decline in the first and second months, but not in the third. Group 3 showed significantly low eosinophiles in each of 4 monthly periods following inoculation. Thus, of eight significant deviations, all were downward and all were in the three

groups receiving the more virulent inoculum. The decline was not dependent on the leucopenic phase, as may be seen in group 3; these animals had no leucopenia (see charts 2 and 3). (The eosinophiles do not disappear entirely, as previously reported by some workers, but are present in such small numbers during severe tuberculosis that often many cells must be counted to find a single eosinophilic leucocyte.)

Lymphocytes: None of the four groups of animals exhibited abnormal values for lymphocytes in the first month after inoculation, as can be

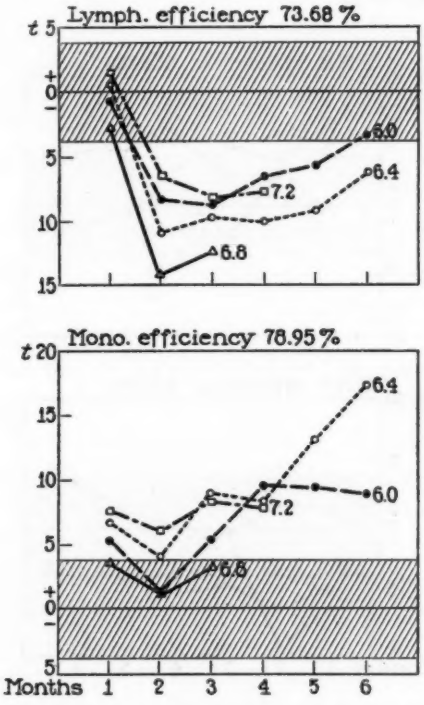

CHART 4. Monthly mean deviations of lymphocytes and monocytes expressed as multiples of their probable error.

seen from chart 4. A significant decline in circulating lymphocytes occurred in each group during the second month. The lymphopenia was marked in each case, but most profound in group 4; it persisted in every group throughout the disease, except in group 1. The latter animals exhibited a fall in lymphocytes, and then a rise, so that by the sixth month the mean value was not significantly low. From chart 4 it may be seen that the curves for lymphocytes more faithfully reflected the

course of the disease than any of the other blood cells, that is, the magnitude of change most closely paralleled the severity of the infection. However, as will be shown, they were less sensitive than the monocytes in that the latter showed abnormal values earlier. Fourteen of the nineteen mean monthly values for lymphocytes following inoculation were significantly low, giving an efficiency of 73.68 per cent for these cells.

Monocytes: The rabbits of group 4 at no time showed significant deviations from the normal counts of monocytes, as shown on chart 4. The absolute values were at all times above the base-line mean (as shown in table 1) but the deviation was not statistically significant. The animals of group 1 exhibited a mean value for monocytes in the second month which was within the normal range. All other monthly mean values in all the groups showed significant deviations in the direction of an increase. Thus, in three of the four groups there was a significant rise in the first month after inoculation, and in two groups this rise persisted throughout the disease. Fifteen of the nineteen monthly mean values for monocytes showed significant elevation, giving an efficiency of 78.95 per cent. Thus these cells were more sensitive than any others in reflecting the course of events; but the fact remains that, in the animals exhibiting the most severe infection, the circulating monocytes did not show an increase of high order.

Neutrophile-lymphocyte ratio: The animals of group 4 at no time showed significant deviation from the mean base-line value for the neutrophile-lymphocyte ratio. In this group there was a rise in the second and third months (table 1) but it proved not to be statistically significant. Group 3 showed significant elevation of the neutrophile-lymphocyte ratio only in the fourth and final month of disease. Again the mean values were elevated in the second and third months, but the rise was not significant as the probable error of the deviation was very high. The two groups receiving the more attenuated cultures showed significant elevation of the neutrophile-lymphocyte ratio during the second to sixth months following inoculation. This elevation was in large part due to the decrease in lymphocytes, since nine of the ten corresponding values for lymphocytes were significantly low, whereas only five of the ten corresponding values for neutrophiles were significantly elevated. Eleven of nineteen mean values showed significant elevation, so that the efficiency of the neutrophile-lymphocyte ratio was 57.89 per cent. But it is important to note that only one of seven mean values following in-

oculation showed significant elevation from the normal in the two groups of animals inoculated with the two more virulent cultures. Deviations of the neutrophile-lymphocyte ratio are shown on chart 5.

Monocyte-lymphocyte ratio: Statistically significant deviations from the normal monocyte-lymphocyte ratio occurred in all the counts following inoculation except in that for the first month in group 4 and that for the second month in group 1. Thus, of nineteen mean values at all stages of the disease, seventeen were significantly elevated. The effi-

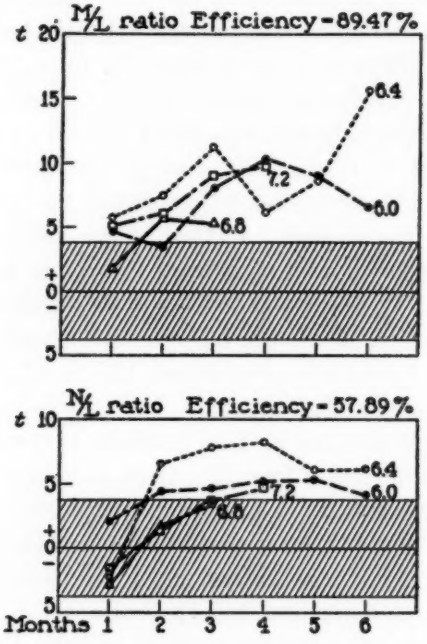

CHART 5. Monthly mean deviations of the monocyte-lymphocyte and neutrophile-lymphocyte ratios expressed as multiples of their probable error.

ciency of this ratio was therefore 89.47 per cent, and it was more sensitive in detecting the presence of infection than the neutrophile-lymphocyte ratio, the haemoglobin, or any of the blood cells considered separately. Furthermore, although the values given on chart 5 show no parallelism with the severity of infection, the actual mean values for the index given in table 1 do show greater change in the groups receiving the more virulent microörganisms, and progressively higher mean values in each group. Table 1 also shows that the mean values for the monocyte-lymphocyte

TABLE 1

Mean normal and mean monthly postinoculation values for each type of blood cell, for the monocyte-lymphocyte and neutrophile-lymphocyte ratios, and for haemoglobin in each of the four groups of animals

	INOCULATED WITH CULTURE GROWN AT pH	BASE-LINE	FIRST MONTH	SECOND MONTH	THIRD MONTH	FOURTH MONTH	FIFTH MONTH	SIXTH MONTH
Haemoglobin	6.0	82.2	*77.2*	81.3	79.6	78.6	*67.5*	*71.1*
	6.4	79.9	*71.7*	78.4	78.2	76.5	*61.1*	*60.8*
	6.8	78.9	*69.7*	*72.1*	77.3			
	7.2	80.5	*74.9*	*75.0*	*72.0*	*61.0*		
Red blood cells	6.0	5,814	5,611	5,887	5,818	5,742	5,567	*5,493*
	6.4	5,597	*5,152*	5,641	5,530	5,329	*5,054*	*4,365*
	6.8	5,683	*5,123*	5,431	5,211			
	7.2	5,691	5,526	5,478	5,307	*4,990*		
White blood cells	6.0	10,030	11,064	9,139	9,433	*11,997*	11,137	*11,988*
	6.4	9,470	10,132	9,592	10,380	*12,380*	*11,888*	*13,705*
	6.8	10,268	*8,654*	*7,083*	9,778			
	7.2	9,969	11,155	9,166	10,851	12,185		
Neutrophiles	6.0	4,345	4,850	4,461	4,287	4,941	4,895	*5,484*
	6.4	4,003	3,727	4,661	*5,181*	*5,942*	*6,591*	*7,068*
	6.8	4,417	*3,094*	*2,931*	5,324			
	7.2	4,687	4,540	4,071	4,776	*6,224*		
Basophiles	6.0	537	*785*	643	642	*870*	*845*	*925*
	6.4	440	*641*	*885*	*709*	757	406	318
	6.8	590	578	772	485			
	7.2	586	*880*	935	*889*	*351*		
Eosinophiles	6.0	154	175	180	150	155	192	210
	6.4	122	*65*	81	84	78	*68*	77
	6.8	147	*64*	*45*	142			
	7.2	156	*102*	*81*	*100*	*67*		
Lymphocytes	6.0	4,108	3,996	*2,864*	*2,945*	*3,165*	*3,066*	3,538
	6.4	3,975	4,062	*2,460*	*2,654*	*2,616*	*2,222*	*3,006*
	6.8	3,971	3,434	*2,030*	*1,948*			
	7.2	3,469	3,732	*2,472*	*2,246*	*1,927*		
Monocytes	6.0	872	*1,230*	963	*1,393*	*2,067*	*2,114*	*2,401*
	6.4	914	*1,619*	*1,479*	*1,753*	*2,954*	*2,575*	*3,221*
	6.8	1,123	1,463	1,251	1,879			
	7.2	1,058	*1,890*	*1,584*	*2,815*	*3,552*		

TABLE 1—*Concluded*

	INOCULATED WITH CULTURE GROWN AT pH	BASE-LINE	FIRST MONTH	SECOND MONTH	THIRD MONTH	FOURTH MONTH	FIFTH MONTH	SIXTH MONTH
Neutrophile-lymphocyte ratio	6.0	1.17	1.36	*1.87*	*1.57*	*1.63*	*1.87*	*1.90*
	6.4	1.15	1.00	*2.13*	*2.22*	*2.45*	*3.77*	*2.47*
	6.8	1.27	1.00	1.50	3.08			
	7.2	1.71	1.47	2.01	2.54	*3.63*		
Monocyte-lymphocyte ratio	6.0	0.236	*0.346*	0.434	*0.500*	*0.712*	*0.820*	*0.853*
	6.4	0.255	*0.438*	*0.653*	*0.723*	*1.307*	*1.387*	*1.113*
	6.8	0.313	0.446	*0.666*	*1.025*			
	7.2	0.372	*0.543*	*0.807*	*1.384*	*1.938*		

Note: Statistically significant deviations from the normal appear in italics. Values shown in ordinary type proved not to be statistically significant deviations from the normal.

TABLE 2

Efficiencies of blood cells and cellular ratios in showing abnormal values in tuberculosis

	PER CENT
Ratio monocytes-lymphocytes	89.47
Monocytes	78.95
Lymphocytes	73.68
Haemoglobin	63.15
Ratio neutrophiles-lymphocytes	57.89
Basophiles	52.63*
Eosinophiles	42.10
Neutrophiles	42.10**
Total white cells	36.84**
Erythrocytes	31.57

* Data open to question as base-line values were lower than those of Casey and Pearce, and of Thomas. Animals may have shown rise in basophiles due to influence of state of maturity.

** Less reliable than might be indicated, since some values were high and others low, indicating that both determinations are subject to variation from a variety of causes, such as tuberculosis of bone marrow, secondary infections, etc.

ratio were invariably elevated following inoculation, whereas only sixteen of the values for the neutrophile-lymphocyte ratio were elevated. The greater efficiency of the monocyte-lymphocyte ratio is therefore borne out by the mean values without resort to statistical formulae.

Table 2 lists in order the efficiency values for each of the blood cells, the haemoglobin, and the two cellular ratios in showing abnormal changes in tuberculosis. These values were obtained by dividing nineteen, the

whole number of mean counts of each type of cell following inoculation, by the number of these counts showing significant deviation from the normal mean, and expressing the result as per cent.

DISCUSSION

There are certain fundamental differences between experimental tuberculosis and pulmonary tuberculosis in man. Fortunately the human being is apparently more resistant than the usual experimental animal. Many humans recover, but inoculation of animals with virulent microorganisms invariably results in death. Moreover, the disease in experimental animals usually becomes generalized in contrast to that in the human, which most frequently involves the lungs and lymph nodes draining them. Furthermore, after intravenous inoculation of virulent microörganisms, experimental animals invariably exhibit lesions in the bone marrow. Such lesions in man occur with less regularity. In view of these facts, it is our opinion that the experimental disease in our two groups of animals receiving the more attenuated microörganisms represented more closely the usual picture in man than did the two groups inoculated with the more virulent microörganisms. The latter have a clinical parallel only in the most rapidly advancing cases of pulmonary tuberculosis, or in patients with acute miliary tuberculosis. It is therefore clear that our experiments include individuals in which any test showing, with some regularity, a significant deviation from the normal may be considered a sensitive test. By the same token, any test showing significant deviation from the normal in all four of these groups of animals may be considered highly efficient and reliable. And if the deviations be consistent in one direction, either above or below the normal, it may be considered that intercurrent factors are less likely to exert an influence than if deviations occur in both directions from the normal. Therefore, the monocyte-lymphocyte ratio may be seen to be more sensitive and reliable as a detector for tuberculous infection than the neutrophile-lymphocyte ratio, the haemoglobin, or any of the blood cells alone. It exhibits statistically significant deviations more frequently and consistently than any of the above, and always in the direction of an increase over the normal. Minimal tuberculosis is capable of influencing the ratio significantly, and the magnitude of the change is roughly proportional to the severity of disease.

The efficiency of the monocyte-lymphocyte ratio in tuberculosis is due

to the fact that the lymphocytes and monocytes are the most sensitive of all the blood cells to tuberculosis, and that the changes in these cells are in opposite direction. While the monocyte proves to be the more sensitive of the two in that it shows change earlier, the decline in lymphocytes more closely parallels the decline of the individual resistance (therefore the advance of the disease) than any of the other cells. The fact that the monocyte-lymphocyte ratio has greater efficiency than the neutrophile-lymphocyte ratio is to be expected, since the denominator in the two is the same and the numerator of the one ratio, the monocyte, has greater efficiency than that of the other, the neutrophile.

In regard to the rôle of the neutrophile in tuberculosis, we are in agreement with Medlar, that the general trend, especially in advanced disease, is for the neutrophiles to increase. It is likewise true that, in the acute tuberculous lesions (41, 42) the neutrophile plays a more important part than in chronic or retrogressive lesions. However, in certain instances, namely, early, severe infection, the neutrophiles may diminish in number, which renders their efficiency less than if the change were in the opposite direction. This early decline in neutrophiles appears not to be caused wholly by lesions in the bone marrow, since all the cells having origin there are not equally affected. There may be neutropenia without anaemia, as shown by the mean values for neutrophiles and for erythrocytes in the group inoculated with the culture grown at pH 6.8 during the second month (table 1). Moreover, our results indicate that an increase in neutrophiles occurs only with well established or advanced disease, whereas the changes in monocytes occur earlier.

It seems probable, for reasons stated before, that the elevated values we have obtained for basophiles are less significant than is apparent. It appears likely that the basophiles are little changed in tuberculosis.

The decline in number of eosinophiles cannot be explained due to lack of knowledge of the function of these cells. While not a sensitive indicator, the decline is quite characteristic in advanced tuberculosis; it does not occur in very mild tuberculosis.

Our results indicate that the anaemia in tuberculosis is of the microcytic type, since the decline in haemoglobin is proportionally greater than the decline in erythrocytes. Also the haemoglobin is more sensitive than the erythrocytes, abnormal values being obtained when the number of erythrocytes was in the normal range. The lesions to be found in the bone marrow seem wholly inadequate to account for the anaemia and leucopenia which occur in severe infection. It seems more likely

that the anaemia and leucopenia are due to toxic effects of products of the microörganisms, as indicated by Sabin, Doan and Cunningham (20).

The report of Boissevain, Forster and Good (44) records results at variance with most recent studies of the blood in tuberculosis. It seems likely that their failure to confirm earlier reports is due to three facts, namely, their series of cases was very heavily weighted in favor of those with far advanced disease (1,171 of 1,569 counts); the questionnaire method of ascertaining the ultimate condition might be open to serious question; and the number of counts per individual was so small that little information could reasonably have been expected. (Their report includes statistical analyses of 1,569 counts of the blood from 431 patients, an average of less than four per patient, taken over a period of 10 years.) We believe, as do others (28), that if blood studies in tuberculosis are to be of value they must be repeated at relatively frequent intervals.

The results which we have obtained indicate that studies of the blood cells are of great value in tuberculosis. While the blood picture can hardly be said to be pathognomonic, it should be of considerable aid in diagnosis. But perhaps its greatest value is in prognosis, since the quantitative changes in the cells are progressive with advancing disease. We have laid no stress on qualitative changes which we believe to be of equal importance. Profound morphological and physiological changes are known to occur among the monocytes (19, 20) and neutrophiles (1, 2, 3). Wiseman and Doan (43) have also demonstrated qualitative changes in the lymphocytes during tuberculous infection. Since each change in the blood cells is an expression of some particular phase of the pathological picture, it seems that careful consideration of each quantitative and qualitative change is more likely to be informative than any blood index in which the identity of such changes is hidden by an arithmetical formula.

SUMMARY

Carefully controlled studies of the blood cells were made in groups of rabbits subjected to tuberculous infection of four grades of severity. The most significant changes noted were as follows.

1. The monocyte-lymphocyte ratio is a more sensitive indicator of tuberculous infection than any of the blood cells alone or the neutrophile-lymphocyte ratio.

2. Of the individual cells, the monocyte is most sensitive in that it is first to show significant change, but the lymphocyte is the more reliable

for prognosis, as the degree of decline is roughly proportional to the severity of the infection.

3. When anaemia occurs in tuberculosis, it is of the microcytic type. The haemoglobin is more sensitive to tuberculous infection than are the erythrocytes.

4. There is a tendency, especially with advanced disease, toward a rise in neutrophiles and a decline in eosinophiles.

5. The basophilic granulocytes are probably little affected in tuberculosis.

6. In very acute tuberculous infection the blood cells may fail to show the changes which are so characteristic of more slowly progressive disease. In such instances the decline in lymphocytes may be the only significant quantitative change.

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THE HISTOPATHOLOGICAL BASIS FOR THE X-RAY DIAGNOSABILITY OF PULMONARY MILIARY TUBERCULOSIS[1, 2]

PAUL E. STEINER

The clinical diagnosis of generalized miliary tuberculosis in suspected cases is often notoriously difficult. If there is a coincident tuberculous meningitis, the diagnosis, in a case otherwise suspicious, becomes highly probable but is not proved. The finding of a retinal tubercle makes the diagnosis certain, but unfortunately such tubercles are not commonly found. The best evidence during life is the demonstration by X-ray of the characteristic mottled or "snow-storm" effect in the lung fields. But this eagerly sought X-ray evidence is absent for some time after the clinical onset in most patients and remains absent during the entire course of the disease in about half of the cases in which pulmonary miliary tubercles are subsequently seen at autopsy. So there are many cases which cannot be definitely diagnosed antemortem in our present state of knowledge.

The question arises as to why only about one-half of the cases give pathognomonic X-ray films. How do the tubercles in the cases which cannot be demonstrated by X-ray differ from those which can? What factors are responsible for the presence or absence of X-ray shadows? Can an understanding of these factors lead to more satisfactory diagnosis and also help the clinician estimate approximately what is going on in the lung, histologically speaking, and thus more accurately estimate the patient's resistance to the infection?

Two factors suggest themselves at once as being important in determining whether miliary tubercles will cast a shadow. They are the size and number of tubercles. According to many investigators these are the only important factors. But observant pathologists know that sometimes lungs with small tubercles produce a positive X-ray film during life, while other lungs with larger tubercles do not. Size, therefore, is not the sole factor. It is also apparent to many pathologists

[1] Presented at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

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that the correlation between the X-ray diagnosability during life and the number of miliary tubercles is not perfect, because X-ray films are sometimes negative in cases in which pulmonary tubercles are very numerous, and typically positive in other cases where the tubercles are less numerous.

If the roentgenological shadow cast by miliary tubercles in the lungs does not depend entirely on the size of the tubercles or on the number which are present, other factors may be important. Miliary tubercles vary greatly in their histological structure and correspondingly in their chemical make-up. The composition of the tubercles may be an important third factor.

The work reported here was undertaken to study some of these relationships by analyzing (*1*) the correlation between the histological structure of miliary tubercles and their X-ray diagnosability during life, and to compare the importance of the histological make-up with the factors of (*2*) the size and (*3*) the number of tubercles in producing shadows. An effort was made to keep the study as objective as possible by using actual measurements and by submitting data to statistical analysis wherever possible.

As a result of these studies it became apparent that a chemical basis, more fundamental than the observed histological basis, was present. The second part of this paper deals briefly with preliminary studies, by the microincineration technique, undertaken to solve this basic chemical explanation for the difference in X-ray shadow of the different types of miliary tubercles.

A. *Comparison of the Histological Structure, Size and Number of Tubercles with the X-ray Diagnosis*

Fifteen cases of generalized miliary tuberculosis autopsied by various members of the Pathology Department of the University of Chicago and thirty-one cases examined by pathologists at the Children's Memorial Hospital of Chicago, a total of forty-six, were studied. On representative microscopical sections of the lungs the average size of the tubercles was measured. From one to five microscopical sections from different lobes of the lungs were available in each case for this determination. Then, on the same sections the average number of tubercles per square centimetre was counted. Any error which might be introduced because of variation in thickness of the microscopical sections from the different cases had to be ignored. The lungs had not been hardened by fixatives before removal and they may have been collapsed

to varying degrees by handling, thus possibly introducing another error. With a series of cases as large as this, errors of both types could neutralize each other in the various groups.

The histological structure of the tubercles was next studied and they were classified according to a scheme devised for this purpose. The following system for histological grading of the miliary tubercles was used:

Epithelioid tubercle ("Soft" tubercle)
Caseonodular tubercle ("Soft" tubercle)
- Grade I—caseation minimal
- Grade II—caseation moderate
- Grade III—caseation predominant

Fibrocaseous tubercle ("Hard" tubercle)
- Grade I—caseation minimal
- Grade II—caseation moderate
- Grade III—caseation predominant
- Grade IV—adult fibrous tissue encapsulating caseous material

Fibroplastic tubercle ("Hard" tubercle)
- Grade I—epithelioid cells still abundant
- Grade II—pure fibrous tissue
- Grade III—adult fibrous tissue with dense collagen

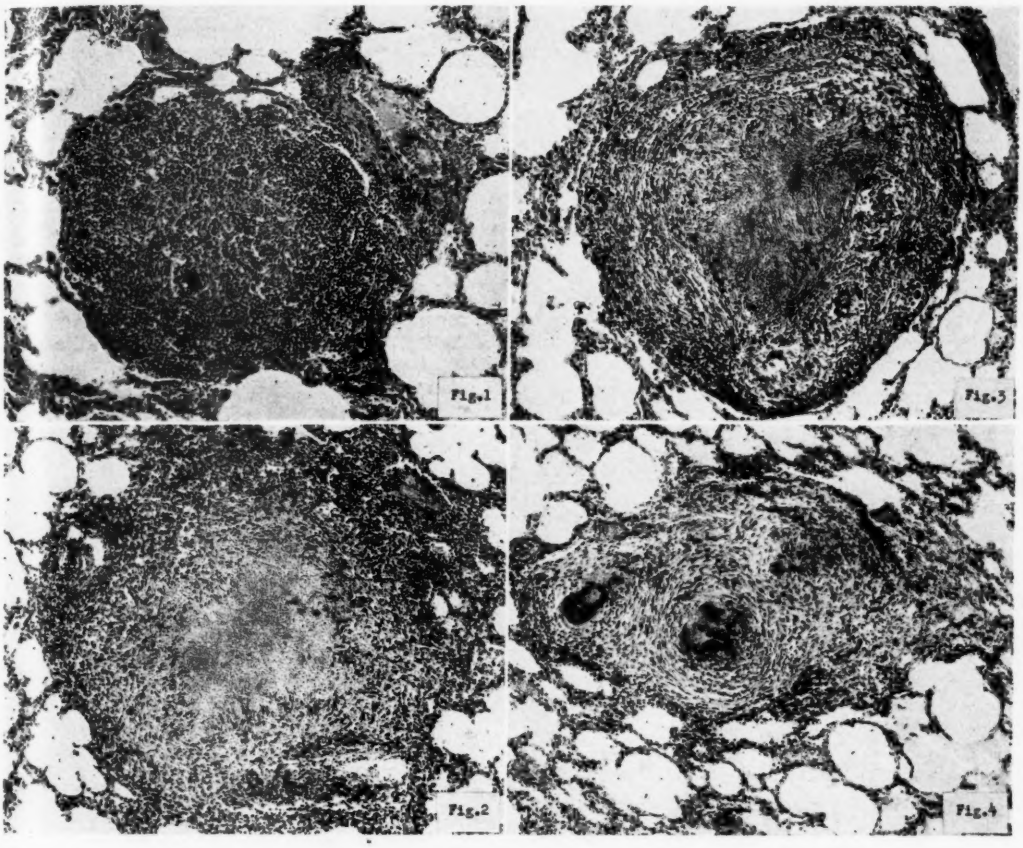
This grading system was interpreted and defined in the following manner.

The epithelioid tubercle is composed predominantly of epithelioid cells. There may or may not be one or more giant cells. Lymphocytes are usually few at the centre but they may be numerous in the marginal zone. If the peripheral epithelioid cells are flattened and arranged concentrically there must be few or no fibrous collagen fibrils among them. (See figure 1.)

Caseonodular tubercles are essentially epithelioid tubercles with varying amounts of central necrosis. Those having only a small amount of central caseation are classified as grade I. If the caseous centre comprises about half of the cross-section diameter of the tubercle it is called grade II. When the area of caseation occupies most of the tubercle and there is only a narrow peripheral zone of surviving epithelioid cells and lymphocytes it is called grade III. (See figure 2.)

Fibrocaseous tubercles are those which have a caseous centre surrounded by fibrous connective tissue. In grade I the caseous area is

small, in grade II it is larger, making up about one-half of the cross-section diameter of the tubercle, and in grade III the caseous centre is large and the fibrous peripheral zone relatively narrow. In each of these three grades epithelioid cells are still present in the fibrous peripheral



Photomicrographs in figures 1 to 4 were all made with a magnification of × 62.5

Fig. 1. Epithelioid type of tubercle
Fig. 2. Caseonodular, grade I to II, type of tubercle
Fig. 3. Fibrocaseous, grade I, type of tubercle
Fig. 4. Fibroplastic, grade I, type of tubercle

zone, whereas in fibrocaseous grade IV the encapsulating zone is dense fibrous connective tissue. (See figure 3.)

Fibroplastic tubercles also have fibrous connective tissue, but there is

no central caseation. Epithelioid cells are still numerous in grade I but the fibrous tissue is abundant peripherally. If the tubercle is composed almost entirely of young fibrous tissue it is rated grade II. If the fibrous tissue is dense and adult the grade is III. This represents an inactive tubercle. (See figure 4.)

The greatest difficulty encountered in trying to apply this grading system was that in a few cases the tubercles were of several ages and consequently they differed in histological composition. In such cases if there was a marked predominance of any one grade of tubercle, that classification was arbitrarily given to all. In several other cases where about equal numbers of one or more histological types were present the "hardest" grade represented was applied to the case. A "hard tubercle" shows fibrous connective tissue proliferation. This indicates resistance to the infection and a healing tendency, and also that the tubercle is old enough for this healing tendency to manifest itself. Thus, in this grading scheme, a fibrocaseous grade I tubercle is "harder" than an epithelioid tubercle, a caseonodular tubercle of any grade, and a fibrocaseous grade III tubercle, but not as "hard" as fibroplastic tubercles of grades II and III. Epithelioid tubercles are considered to be "soft" tubercles. They may become "hard" tubercles of fibroplastic type if the resistance is good. Or they may undergo central caseation if resistance is poorer, thus becoming caseonodular tubercles. They may later become "hard" tubercles by conversion of the caseonodular tubercle into a fibrocaseous one.

In some cases the microscopical sections were small. If it was felt that they were not adequate in conjunction with the description of the distribution of tubercles as recorded grossly at autopsy, to make a fair determination of the number per square centimetre, such cases were not included in making up the tables. Consequently those tables in which the number of tubercles is a factor under analysis have fewer cases than do the others.

It was not necessary to make a place in the grading scheme for calcific tubercles because no examples were encountered in this study. Miliary tubercles are so small that, if the patient survives, the tubercles usually heal by complete fibrous organization rather than by fibrous encapsulation of a caseous centre with subsequent visible calcium infiltration of the caseous material.

After the cases used in this survey had been repeatedly reviewed, the histological classification of the tubercles made, the number of tubercles

per square centimetre counted, and the average size of the tubercles measured, the X-ray films were examined for the first time. The written diagnosis which had been made by the X-ray departments was compared by the writer with the appearance of the films. If there was any disagreement regarding the interpretation of the films, they were resubmitted to the X-ray diagnosticians, whose final diagnosis was always accepted. The few films which they reported as "highly suspicious" of miliary tuberculosis were accepted as positive in compiling the final result. Only cases in which there had been an X-ray examination in the last few days of life were suitable for this study. It was necessary that the histological composition of the tubercles did not have time to undergo much change after the last X-ray film was made. This criterion alone eliminated many cases which would have been suitable otherwise. Cases with marked pleural or pulmonary lesions, aside from the miliary tuberculosis, likewise had to be discarded because the lung fields were obscured.

The result of the correlation between the histological types of miliary tubercles and the X-ray diagnosis is given in table 1. These results tentatively indicate that there is a definite correlation of the X-ray diagnosability and the cellular composition of the tubercle. Epithelioid tubercles do not cast a shadow, while if either collagen fibrils or caseous material are present a shadow will probably be cast. That the shadow is not due solely to the caseous material in the tubercle is shown by the case classified as fibroplastic grade I. In this instance the "snow-storm" effect on the X-ray film was characteristic but there were no tubercles with caseation on microscopical examination. The tubercles were small varying from those of microscopical size to others 0.75 mm. in diameter. They were quite fibrous.

The correlation between the number of tubercles per square centimetre and the X-ray shadow cast by them is shown in table 2. It shows that when there were twenty or fewer tubercles per square centimetre about half of the cases were positive on X-ray. But as the tubercles increase in number the proportion of positive X-ray diagnoses does not show a corresponding rise. The number of cases in each of these groups is too small to permit reliable deductions; the cases studied were about equally divided between positive and negative. There is imperfect correlation between the number of tubercles per unit surface of sections and the X-ray diagnosability.

When all cases with less than twenty tubercles per square centimetre

are subdivided into two groups, one containing ten or less and the other eleven to twenty as shown in table 2A, evidence is given that if tubercles are very few the films are likely to be negative. The explanation is that in these cases the tubercles are mostly epithelioid.

The correlation between the size of the tubercles and the X-ray shadows which they cause is presented in table 3. When the tubercles are under one millimetre in size the X-ray films are not diagnostic in two-thirds of the cases while in the other third they are typical. The films are diagnostic in over half of the cases in which the average size of the tubercles was between one and two millimetres, but this size alone was

TABLE 1

Correlation of histological grading with X-ray diagnosis

TYPE OF TUBERCLE	POSITIVE X-RAY	NEGATIVE X-RAY
Epithelioid	0	16
Caseonodular	13	5
Grade I	5	1
Grade II	6	3
Grade III	2	1
Fibrocaseous	8	2
Grade I	6	1
Grade II	1	1
Grade III	0	0
Grade IV	1	0
Fibroplastic	1	1
Grade I	1	1
Grade II	0	0
Grade III	0	0

not enough to insure a positive film. Pulmonary tubercles of haematogenous miliary type do not often become larger than this. The average size of the tubercles, therefore, shows some correlation with the X-ray diagnosability but this is even less perfect than is the number of tubercles.

A study of table 1 might suggest to some that the reason why epithelioid tubercles do not give a positive film is perhaps their smallness, and that large caseonodular and fibrocaseous tubercles yield a high percentage of positives only on account of their size. To analyze the importance of size as compared with histological composition table 4 was

made. On it, three factors are studied. The histological nature of the tubercles, the X-ray appearance and the average size of the tubercles are plotted. The table shows that most epithelioid tubercles are small but even the larger ones do not have positive films. In caseonodular tubercles positive and negative X-ray films are evenly distributed in all size groups. In fibrocaseous tubercles the same is true, although the cases with negative X-rays are so few (two cases) that the spread shown might not be generally true. This chart shows that epithelioid tubercles

TABLE 2

Correlation of number of tubercles with X-ray diagnosis

NUMBER OF TUBERCLES PER SQUARE CENTIMETRE	POSITIVE X-RAY	NEGATIVE X-RAY
1–20	9	12
21–40	6	1
41–60	3	2
61–80	2	2
81–100	1	0
141–160	1	0

TABLE 2A

1–10	2	8
11–20	7	4

TABLE 3

Correlation of size of tubercles with X-ray diagnosis

AVERAGE SIZE OF TUBERCLES	POSITIVE X-RAY	NEGATIVE X-RAY
Under 1 mm.	9	17
1–2 mm.	11	7
2–3 mm.	1	0
Over 3 mm.	1	0

do not give negative films merely because they are all small. It further shows that in the case of caseonodular, fibrocaseous and fibroplastic tubercles size is not the determining factor as to whether films are positive or negative.

A study of table 1 might suggest that perhaps epithelioid tubercles do not produce positive films because tubercles are too few in number, and that caseonodular and fibroplastic tubercles produce positive films because of greater numbers of tubercles. Table 5 was made to analyze

this possibility. Three factors are studied. This time, the histological nature of the tubercles, the X-ray appearance and the average number of tubercles are plotted. The table shows that many cases classified as epithelioid have few tubercles, but that those with great numbers, namely, fifty and seventy-five, are also negative. The number distribution in the caseonodular and fibrocaseous groups is greater, but in each group a case with few tubercles (ten per square centimetre) had a posi-

TABLE 4

Size distribution of tubercles of each histological type and X-ray result

TYPE OF TUBERCLE	X-RAY	SIZE OF TUBERCLES			TOTAL
		Under 1 mm.	1–2 mm.	Over 2 mm.	
Epithelioid	Positive				
	Negative	00 00 0 0 0 0 00 0 0 0	00 0		16
Caseonodular	Positive	+ + + + + + + + +	+ + + + +	++	13
	Negative	0 0	0 0 0		5
Fibrocaseous	Positive	+ +	+ + + + + +		8
	Negative	0	0		2
Fibroplastic	Positive	+			1
	Negative	0			1

tive film. On this chart again, the histological composition of the tubercle shows by far the closest correlation with the X-ray appearance.

In summary, the tables show that the histological composition of pulmonary miliary tubercles, a factor hitherto neglected, is of greater importance in determining whether the X-ray films are diagnostic or not than are the factors of size or of number of tubercles, which have in the past been considered to be so important.

B. *Correlation of the Histological Structure with the Chemical Composition of Miliary Tubercles*

From the work reported in the preceding section it became apparent that either caseous material or collagen or both were present in the miliary tubercles when the X-ray was positive. Morphologically considered, the reason for this was not readily apparent. In no case did the caseous material contain sufficient calcium to be visualized by the usual tissue stains. Furthermore, in many of the cases with caseonodular tubercles,

TABLE 5

Number distribution of tubercles of each histological type and X-ray result

TYPE OF TUBERCLE	X-RAY	NUMBER OF TUBERCLES PER SQUARE CENTIMETRE								TOTAL
		1–10	11–20	21–40	41–60	61–80	81–100	141–160		
Epithelioid	Positive									
	Negative	0 0 0 0 0 0	0 0	0	0	0				12
Caseonodular	Positive	+	++ + +	++ +	+	+	+			13
	Negative	0	0							2
Fibrocaseous	Positive	+	++	+ +	+ +			+		8
	Negative		0		0					2
Fibroplastic	Positive					+				1
	Negative					0				1

the caseation necrosis had occurred relatively shortly before death as estimated both from the age by the clinical history and the histological appearance of the tubercles. It was hard to understand how such tubercles could have had an appreciable acute infiltration of calcium. In one case where the X-ray film was positive the tubercles were fibroplastic, so connective tissue itself must have some ability to cast a shadow.

The mottled or "snow-storm" effect seen on typically positive X-ray films is caused by uneven exposure of the film. This in turn must be due

to the fact that nearly parallel beams of X-rays leaving the target in the X-ray tube have been absorbed to different degrees on passing through the body. Ability to absorb or stop X-ray beams varies with the atomic weight of the atoms in the tissue and not with the molecular weights.

With these ideas in mind, microincineration of tubercles of the various histological types was done. Lung tissue from thirteen of the cases used in the first section of this study were imbedded in celloidin by the usual technique. Five serial sections of the same thickness were cut. Of these, serial section number one was stained by the Cooper modification of the Ziehl-Neelsen stain. When properly performed this stain gives excellent cytological detail in addition to staining the tubercle bacilli. Serial section number two was ashed by incineration. Serial section number three was stained with haematoxylin and eosin, section number four by Mallory's connective tissue stain, and serial section number five by Van Gieson's method for connective tissue.

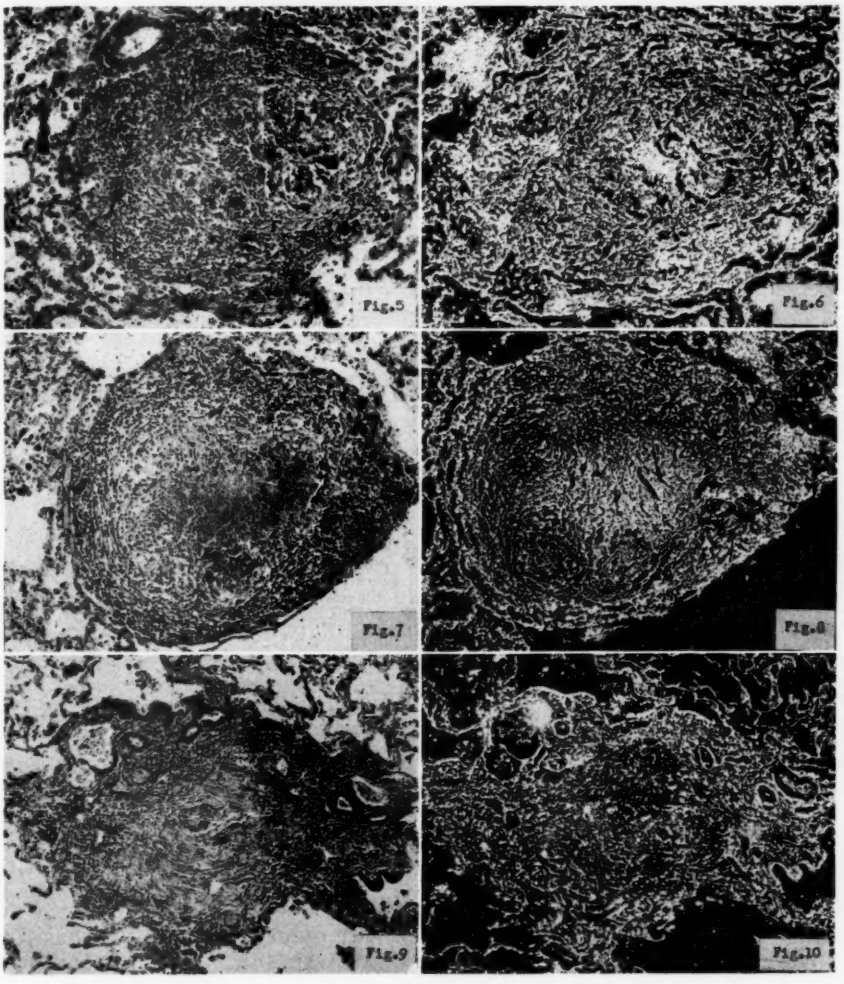
Microincineration was carried out by ashing the sections in a muffle furnace after the celloidin had been removed. The temperature was gradually elevated over a period of several hours to a maximum of 560° C. The temperature was above 500° C. for over an hour and a half. By this method all organic matter was burned and the inorganic ash of the cells remained as a fine deposit on the glass slide. The distribution and amount of this residue was studied under the microscope.

By the use of this serial section technique, tubercles of each histological type were identified on the stained sections and the same tubercles studied on the corresponding incinerated slide.

The incinerated epithelioid tubercle shows the greatest amount of ash in the outer cellular regions, where cell nuclei are most numerous. (See figures 5 & 6.) In the inner regions, where epithelioid cells predominate, nuclei are farther apart because the cells have more cytoplasm, and there is slightly less inorganic ash. The illustration shows a small area in the very centre in which there appears to be more ash but this appearance is deceiving. Direct microscopical examination shows that the ash is merely more evenly distributed and not more abundant. By the method of illumination used in making the photomicrograph this is made to appear denser.

The incinerated fibrocaseous tubercle shows essentially the same sort of mineral distribution. (See figures 7 & 8.) The area seen to be caseated, on direct examination, has less ash but it photographs as having more with this type of illumination because the deposit is so fine and so evenly distributed.

The very fibrous tubercle containing anthracotic pigment has least ash in regions of most dense collagen and greater amounts where nuclei are numerous. (See figures 9 & 10.)



Photomicrographs in figures 5 to 10 were all made with a magnification of × *62.5*

Fig. 5. Haematoxylin and eosin stained
Fig. 6. Incinerated epithelioid tubercle
Fig. 7. Haematoxylin and eosin stained
Fig. 8. Incinerated fibrocaseous tubercle
Fig. 9. Haematoxylin and eosin stained
Fig. 10. Incinerated fibroplastic tubercle

These incineration studies give information only about the amount of ash and not about its chemical nature. They do not reveal the cause for

the correlation between the histological structure of tubercles and their ability to cause X-ray shadows. The possibility still exists that the ash deposited by collagen and caseous material, although it is not greater in amount, has atoms of a higher atomic weight. This could explain the difference in the X-ray result.

DISCUSSION

In this study no allowance was made for variable or possible inadequate X-ray technique. The roentgenological departments at both hospitals take great pride in their diagnostic acumen, and it is the opinion of the writer, as well as of others, that the X-ray diagnostic work at both institutions is of a high order. Furthermore, variations in technique would probably not explain the group differences encountered in this study.

The differences observed in the X-ray diagnosability of tubercles of different histological types apply only to lungs *in situ*, as far as this report goes. No study was made of the shadows cast by the tubercles in excised lungs. It is probable that such studies would not confirm the results reported here. In such preparations the absorption of X-rays by the anterior and posterior body walls, structures probably responsible for most of the total absorption, would not be present. In excised lungs the factors of hardness of rays would be different from those used with the lungs in the body and the results might be different for that reason.

In reviewing the clinical histories of these cases an attempt was made to correlate the X-ray diagnosability with the duration of the disease. This could not be done because it was impossible to ascertain the time of the miliary seeding in the lung by study of the clinical histories. Most of these cases were children and most of them had a coincident tuberculous meningitis. The clinical onset was usually that of the tuberculous meningitis. In many instances histological evidence was that the pulmonary tubercles were older than the tuberculous meningitis.

To the roentgenologist the results of this study may suggest the possibility of more accurate diagnosis by altering the technique in use at present. Whether this will consist of softening the X-rays or using filters to remove certain of the harder rays are matters for experts to decide.

To the clinician this study may prove to be of value in several ways. Perhaps the roentgenologist will be able to make a positive diagnosis for

him in a higher percentage of instances. With the X-ray technique in use at present he will know that the tubercles are past an epithelioid stage if the X-rays are positive.

An outstanding weakness in this study is the small number of cases. With a series of several hundred, significant differences in the subgroups might lead to a more accurate explanation of the observed findings. The writer hopes that some one with a greater number of cases will pursue such studies.

SUMMARY

A comparison of the X-ray films of patients dead of miliary tuberculosis, with the number, the average size and the histological structure of the tubercles in the lungs revealed the latter factor to show the best correlation with the X-ray appearance. The antemortem X-rays were negative in all cases in which the tubercles were epithelioid, whereas in cases with tubercles containing caseous material or collagen or both, the X-rays were usually positive. The chemical explanation for this observation is not known. None of the tubercles contained visible calcium on the routine stains, and microincineration of tubercles of the various histological types revealed no significant quantitative difference in ash. By using softer X-rays or by selective filtration of X-rays of certain wave-lengths, epithelioid tubercles might produce positive films.

The author is indebted to Dr. Joseph Brenneman, Dr. Wm. G. Hibbs, and Dr. Wm. E. Anspach of the Children's Memorial Hospital staff for permission to use their records, and to Mr. Louis Cohen for assistance in the earlier part of this study.

NONCASEATING TUBERCULOSIS[1,2]

A Preliminary Report

MAX PINNER

This report is a brief summary of a rather lengthy analysis of the literature which was made in connection with a few patients that we had the opportunity to observe and whose detailed case reports will be published later. The brevity of this preliminary report necessitates apodictic statements which will be fully documented and elaborated in a later publication.

The purpose of this preliminary report is to discuss briefly and outline the domain of those forms of tuberculosis that are distinguished by the absence of caseation.

The essential histological entity of noncaseating tuberculosis is the epithelioid-cell tubercle with or without giant cells, with or without marked tendency to fibrosis, but always characterized by the absence or extreme paucity of any other cellular reaction but epithelioid proliferation. There is no or practically no exudation; both polymorphonuclear and lymphocytic reactions are absent. This lesion should be fairly well known under the name of tuberculous large-cell hyperplasia (Ziegler). Anybody who has tried to prepare slides for teaching, showing this lesion which is illustrated in practically all textbooks as the typical young proliferative tubercle, knows how extremely rare this lesion is, in human material at least. It is found occasionally in some cases of miliary tuberculosis, sometimes in excised lymph nodes from cases in which the clinical differential diagnosis comprises usually all pathological processes known to cause enlargement of lymph nodes, and probably most frequently in skin biopsies. Parenthetically it may be mentioned that this lesion is less rarely seen in spontaneous and experimental tuberculosis in some of the more tuberculosis-resistant animals.

These epithelioid-cell tubercles may apparently exist over long periods

[1] Presented at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

[2] From the District State Tuberculosis Hospitals of the New York State Department of Health, Ithaca, Mount Morris and Oneonta, New York.

of time without showing any essential changes; or they may heal, probably by absorption, and certainly by fibrotic transformation; the fibrosis in these cases shows particularly coarse and broad fibres and progresses to complete hyalinization.

A further characteristic of these lesions is the fact that acid-fast rods cannot usually be found in them and that more often than not they are sterile both in cultures and in animal inoculation.

For quite some time the most characteristic representative of this lesion was exclusively the concern of the dermatologist: Boeck's sarcoid or benign miliary lupoid; and the more or less closely associated conditions, such as *lupus pernio*, Darier-Roussy's subcutaneous sarcoids, angiolupoid and probably Bazin's disease. However, even strictly dermatological examinations revealed the fact that the majority of patients presenting these skin lesions had lymphadenopathy; further studies showed that more frequently than not they had characteristic cystic lesions in the small bones, that many had mediastinal lymph node swellings and disseminated parenchymal foci in the lungs. Finally, by direct or indirect evidence, the conclusion was reached that hardly any organ is immune. Out of the dermatological affection, benign miliary lupoid, the concept of a generalized disease, "Boeck's disease," had developed. And, if general clinical behavior and typical histological findings be accepted as criteria of a nosologic entity, it is fully justified to state that Boeck's disease may manifest itself by lesions in almost all or any organ; it may be confined to the skin only; it may involve lymph nodes, lungs, bones, spleen, mucous membranes, muscles and so on; and skin lesions may be completely absent.

For some time certain forms of pulmonary lesions, with and without hilar lymphadenopathy, have been reported that have certain general characteristics in common. They are fairly symmetrically distributed, they may consist of small, almost miliary, or of larger foci. The paucity of symptoms and signs is in striking contrast to the extent of the anatomical involvement. They may show slow transformation into diffuse fibrotic lesions or they may apparently resorb. Tubercle bacilli are either very difficult to demonstrate or apparently absent. These forms have been described under a variety of names; *granulie froide*, *granulie discrète*, *miliaris discreta*, chronic miliary tuberculosis, tuberculids of the lungs, etc. Morphologically and clinically these pulmonary findings are identical with those so frequently seen in patients with *lupus pernio*, Boeck's sarcoid or certain tuberculous affections of the eye. This close

clinical and roentgenological similarity is probably ample justification for considering these lesions as belonging to essentially the same nosologic unit as Boeck's disease, noncaseating tuberculosis, particularly since associated lymph node lesions frequently show typical epithelioid-cell tubercles.

A trend of studies starting with roentgenological observations reached identical conclusions. The cystic bone lesions mentioned before were described by Jüngling under the name of *ostitis tuberculosea multiplex cystoides*. They are undoubtedly one of the more common manifestations of Boeck's disease or, preferably, of noncaseating tuberculosis.

For a good many reasons that cannot be discussed within the given time limit, it seems quite likely from a study of the literature that so called uveoparotid fever belongs in the same general classification of noncaseating tuberculosis, and the same is true of certain cases showing Mikulicz syndrome.

What is the justification for grouping all these different affections under one heading? There are clinical, histological and biological justifications. Clinically all these diseases are rather benign, chronic and show a certain tendency to intermittence and recurrence. Their common bond is emphasized by the rather frequent occurrence of borderline cases, of cases that overlap more than one disease entity, such as Boeck's sarcoid with iritis, uveoparotid fever with swelling of lachrymal glands and with the same disseminated pulmonary lesions seen in Boeck's sarcoid; peripheral lymphadenopathy with cystic bone changes. The most important link, however, is the fact that the pulmonary changes described above occur in a considerable percentage of all patients primarily diagnosed as Boeck's sarcoid, *lupus pernio, ostitis tuberculosea multiplex cystoides*, uveoparotid fever and generalized adenopathy showing noncaseating epithelioid-cell tubercles.

Histologically, as far as the material is available, there is not only uniformity, but monotony in regard to these lesions. The studies are incomplete, particularly as far as the internal organs are concerned, since with the benignity of the disease, death and autopsies are rare. The haematological manifestation of the epithelioid proliferation is the frequent monocytosis in these diseases.

Biologically it is of interest to note that a large percentage of all these patients, as far as they were tested, react only slightly or not at all to tuberculin. However, this is apparently not the anergy of the noninfected organism, since in a respectable number of patients it was possible

to show that they have tuberculin-neutralizing substances (so called anticutines) in their serum.

What is the justification to assume that the aetiological agent in this group of diseases is the tubercle bacillus?

It must be admitted from the outset that this rests on still sparse direct evidence and on much circumstantial evidence. In the vast majority of lesions on which bacteriological studies have been made, no acid-fast or other organisms have been demonstrated. In a few cases tubercle bacilli were found. But the particular conditions under which positive and definite results were obtained provide probably the explanation for the far more frequent negative results. Positive findings are almost completely restricted to studies on very young lesions, and serial observations showed that tubercle bacilli were present only during the first two weeks of the life cycle of these lesions.

The circumstantial and indirect evidence for the aetiological nature of these diseases comprises: (*1*) the histological characteristics of the lesions; (*2*) the demonstration of anticutines and therewith of positive tuberculin anergy; and (*3*) the fact that practically all patients who died, died of frank tuberculosis. In some of the autopsy findings the slow and gradual transformation of the characteristic epithelioid-cell tubercles into banal caseating bacilliferous tuberculosis is most suggestive.

It is, then, probably permissible to indicate in approximate outlines the biological entity of noncaseating tuberculosis which manifests itself under the variety of the clinical pictures mentioned above. It is a tuberculosis with wide-spread haematogenous lesions in which an unusually stable balance is established between host and parasite, in which therefore symptoms are inconspicuous in comparison with the anatomical involvement. This balance is expressed by positive anergy and absence of caseation and an efficient mechanism for checking bacillary growth. The particular characteristics of this type of tuberculosis may be dependent on the internal milieu of the host or on specific peculiarities of the parasite. I incline to the belief that the former factors are more important in determining the type of disease, chiefly for two reasons: (*1*) as mentioned before, certain tuberculosis-resistant animal species tend toward the development of noncaseating tuberculosis when infected; and (*2*) in those human cases in which the noncaseating lesions finally undergo caseation, it is suggestive that the strain of infecting bacilli remained the same but that the terrain in which they lived has changed. But before this question can be decided many more data must be available. It is hoped that this report will stimulate further observations in this field.

BRONCHIECTASIS ASSOCIATED WITH TUBERCULOUS BRONCHIAL OBSTRUCTION[1]

SUMNER S. COHEN AND GEORGE K. HIGGINS

Tuberculous bronchial obstruction complicating pulmonary tuberculosis has received much attention in the past few years. Series of cases have been reported by Eloesser (1), Epstein and Ornstein (2), Samson (3), Vinson (4), Phelps (5) and Andrews (6); while single cases have been published by Crimm and Strayer (7), McConkey (8), Werner (9) and others. Most of the obstructions described have been mural in type, produced by submucous tuberculomata, granulations or cicatricial stenoses of the trachea or major bronchi. Our experience, described by Phelps, is in accord with the findings of most of the authors quoted. The morbid anatomy of this type of obstruction has been discussed by Eloesser.

The bronchial changes found distal to the obstruction have not received as much attention as the obstruction itself. We believe these bronchial changes must be considered when planning the treatment for any patient whose pulmonary tuberculosis is complicated by tuberculous bronchial obstruction and bronchiectasis. Eloesser states, "More often than not, both at the bedside and autopsy table, stenoses are complicated by suppurations and infections which lie distal to the stenosis. Septic secretions, able to drain imperfectly or not at all, give rise to abscess cavities, bronchiectasis, with purulent content, and to inflammatory swellings and congestion, which mask and complicate the picture of simple stenosis." Andrews mentions the postmortem findings of bronchiectasis distal to a tuberculous bronchial obstruction in one patient. Werner reports one case with a similar type of obstruction and states that signs and symptoms of chronic bronchitis were present. In this patient tubercle bacilli were found in the sputum. Bucker (10) reports a three year old child with bronchial obstruction who died of miliary tuberculosis. Postmortem examination revealed a perforating tuberculous lymph node with cicatricial constriction of the lower lobe bronchus

[1] From Glen Lake Sanatorium, Oak Terrace, Minnesota, and University of Minnesota, Minneapolis, Minnesota.

and bronchiectasis distal to the obstruction. Phelps, who has bronchoscoped all the patients reported in this paper, states, "Suppuration, then, occurs distal to the stenosis and bronchiectasis develops, which may be tuberculous or not."

Warner (11) discusses the important factors in the development of bronchiectasis. Bronchial obstruction and infection of the bronchial wall, with injury or destruction of the muscular and elastic coats, were found at four postmortem examinations at Glen Lake Sanatorium. In addition, destruction of the bronchial mucosa and cilia probably resulted in stagnation of secretion and further infection of the bronchial wall. In many cases, atelectasis, with its traction on the weakened bronchial wall, aids in the development of bronchiectasis. Bronchiectasis, associated with bronchial obstruction, is not limited to tuberculosis. Farrell (12) reported a study of 100 cases of bronchiectasis and found seven following bronchial obstruction, three produced by carcinoma of the bronchus, and four by foreign bodies. Warner in a study of 110 similar cases found three per cent secondary to bronchial obstruction caused either by foreign bodies or carcinomata.

The symptoms indicative of simple stenosis are wheezing, stridor, usually inspiratory, and dyspnoea. The wheezing is most suggestive if it is more or less constant. Frequently a diagnosis of bronchial asthma is made erroneously, on the basis of wheezing and dyspnoea. The dyspnoea may be present when the obstructive lesion is unilateral and the contralateral lung appears normal. Occasionally these patients have attacks of suffocation with severe dyspnoea, audible stridor, cold sweats and cyanosis. These may be due to tenacious sputum lying in the trachea and partially occluding the main bronchus of the unobstructed side. Bronchiectasis should be suspected when the patient has cough and expectoration, especially if excessive, despite apparent control of the parenchymal lesions. Intermittent or constant attacks of fever and other symptoms of general toxicity, due to inadequate sputum drainage, are not uncommon. Coarse and moderately coarse bubbling râles, as well as rhonchi, may be present.

The diagnosis of bronchiectasis is made usually by instillation of iodized oil passively or through the bronchoscope. The obstruction itself may be demonstrated by the oil. We have had no serious reactions following its administration and feel its use is warranted whenever indicated. Neuhof (13), Murphy (14), Cabitt, Singer and Graham (15) have published interesting bronchographic studies with lipiodol in pa-

tients with chronic pulmonary tuberculosis. When bronchiectasis is present, lipiodol is often beneficial in controlling symptoms. The cough and expectoration may be increased for two or three days and then may be markedly decreased for a period of weeks.

Bronchoscopic examination permits visualization of the obstruction and estimation of the degree of suppuration distal to it. We feel that bronchoscopic examination is invaluable not only for diagnosis but also for local treatment. Clerf (16) believes bronchoscopy is of value in complicated cases of pulmonary tuberculosis although he feels its greatest value is in diagnosis. He considers pneumothorax, severe haemoptysis, extensive pulmonary involvement and laryngeal tuberculosis to be contraindications to bronchoscopy, but states the importance of the indication deserves consideration. Nine patients with unilateral pneumothorax have been bronchoscoped in our clinic with no ill effects. Myerson (17) reported bronchoscopic examination of 60 patients known to have, or strongly suspected of having, pulmonary tuberculosis, and in none was there demonstrable spread of the disease. Rice (18) concludes that bronchoscopy is of value primarily for diagnostic purposes. According to Tucker (19) the presence of pulmonary tuberculosis is not a contraindication if local treatment of the tracheobronchial tree is necessary. Vinson (20) states that bronchoscopy should not be performed in the presence of pulmonary tuberculosis unless there is clinical evidence of bronchial or tracheal obstruction. On the whole, it may be stated that bronchoscopic examination is a relatively safe procedure in the presence of pulmonary tuberculosis and should not be withheld when indicated.

In several of our patients with apparently satisfactory collapse, continued cough and excessive expectoration have made us suspect bronchial obstruction with bronchiectasis. When the cough is associated with wheezing, stridor, coarse râles or rhonchi, bronchiectasis is probably present. Tubercle bacilli were found often in the sputum either by direct examination or guinea-pig inoculation. The question may be raised whether these bronchiectases are tuberculous. At first we thought they were nonspecific infections secondary to tuberculous bronchial obstruction but, in studying our postmortem series, tuberculosis was present in the bronchiectatic sacs in all four specimens.

Treatment of the bronchial obstruction has been satisfactory in only a few cases. Dilatation, cauterization and aspiration by bronchoscopy is beneficial but not usually curative. This is true especially in the

cicatricial stenotic-end stage. At times, the obstruction must be disregarded and treatment directed toward relief of the bronchiectasis by direct surgical methods, such as primary lobectomy or cautery lobectomy. Pneumonectomy may be considered when more than one lobe is involved.

Collapse therapy in patients having tuberculous bronchial obstruction must be used with caution. It would be ideal to recognize all the obstructive cases prior to collapse therapy, but the diagnosis often is not made until the collapse has been completed and a satisfactory end-result not obtained. It is discouraging to close a tuberculous cavity in the upper lobe by pneumothorax or thoracoplasty and have the patient continue coughing and raising sputum, frequently containing tubercle bacilli, and then find a bronchiectasis in the base. We are now trying to evaluate carefully signs and symptoms so that bronchial obstruction and bronchiectasis, if present, may be diagnosed before collapse therapy is undertaken. It is our opinion that collapse therapy has nothing to do with the development of obstruction or bronchiectasis. Collapse therapy, we believe, is still indicated in patients with bronchial obstruction provided the bronchiectasis is not advanced. This is true especially of pneumothorax following a recent atelectasis. These patients appear to develop less bronchiectasis, due probably to the relaxation of the bronchial wall by the pneumothorax.

V. Schrötter's (21) mural type of tuberculous bronchial stenosis, in our experience, has been produced by granulation tissue and the cicatricial narrowing of the bronchial lumen by fibrosis. In the latter, the tuberculous involvement of the bronchial wall has progressed to such an extent that the bronchus, from the mucosa to the adventitia, has been completely fibrosed; the mucosa, glands, muscle and elastic fibres are almost absent while the cartilagenous rings are represented by small fragments in the dense connective tissue. The wall is rigid, thick, and the lumen frequently funnel shaped. The marked fibrosis probably represents an end stage in the tuberculous process involving the major bronchi.

The granulation tissue may extend across the narrowed bronchus, reducing its size or even occluding it, as shown in case 1. This membrane was found in two of the four patients upon whom necropsies were performed and appears to be present in about one-half of those described in the literature.

As would be expected in conditions which narrow the lumen to such an extent, bronchiectasis was always present. The suggested reasons

for this have already been mentioned. The lesions encountered in our postmortem specimens have demonstrated to us that tuberculous bronchiectasis can and does occur.

REPORT OF CASES

We have observed nineteen patients with mural bronchial obstruction complicating pulmonary tuberculosis. In thirteen of these bronchiectasis was demonstrated either by lipiodol instillation or necropsy examination. In four additional patients, bronchiectasis has not been demonstrated although symptoms are present. In only two of the nineteen was there a simple stenosis without symptoms or evidence of bronchiectasis.

Case 1: M. O., a woman of 29, developed pleurisy following a cold in April, 1931. She was sent to a sanatorium in July, 1932, where pneumothorax was instituted on the left side. She improved until August, 1933 when she began to have fever, intermittent cough and wheezing. Her condition remained stationary until June, 1935 when severe coughing and choking spells accompanied by rattles in the chest, dyspnoea and cyanosis developed. A diagnosis of bronchial asthma was made. She was transferred to the University of Minnesota Hospital for bronchoscopy and further study. Skin tests revealed nothing definite. While in the hospital she had one attack of severe dyspnoea, cyanosis and unconsciousness. She was resuscitated by artificial respiration and oxygen inhalations. On admission to Glen Lake Sanatorium, June, 1936, the right lung appeared normal; the left showed moderate impairment with diminished transmission of the whispered and spoken voice. The diaphragm was elevated, and scattered coarse râles were heard. There was an inspiratory and expiratory stridor. Roentgen examination revealed a homogeneous density of the left lung with some pneumothorax and a fluid level at the second rib anteriorly. The heart and aorta were displaced to the left (figure 1). Tubercle bacilli were found in the sputum. She was seriously ill with severe paroxysmal cough and expectoration up to 180 cc. daily. Dyspnoea and cyanosis were present constantly. Bronchoscopy, soon after admission, revealed granulations on the left wall of the trachea near the carina with apparent occlusion of the left stem-bronchus by a web of granulation tissue. In August, an atelectasis of the right upper lobe developed. Her condition became progressively worse and she died on September 24, 1936.

Postmortem diagnosis: Fibrous and caseous tuberculosis of the lungs; tuberculous pneumonia; tuberculous empyema; tuberculous bronchial stenosis with bronchiectasis distal to the occlusion; bacterial endocarditis of the aortic valve.

The lungs weighed 1,845 gm. The left was about one-third the size of the

right. Although 2,500 cc. of Kaiserling solution was injected through the trachea, no fluid entered the left lung.

The trachea and the right main bronchus appeared normal, but at the carina the left main bronchus was completely occluded by a thin membrane which was torn when the bronchus was opened. The lumen was narrowed to less than 5 mm. in diameter from the bifurcation of the trachea to the hilum, where the opening again became normal in size (figures 2 & 3). The wall was thickened and fibrous, and the bronchial rings were represented by islands of cartilage. The mucosa, from the carina to the bronchiectatic sacs, was replaced by granulations. The lobar bronchi were slightly thickened by peribronchial "cuffing" of tuberculous tissue. Saccular bronchiectatic cavities, containing small tubercles on their walls, had replaced nearly all of the pulmonary parenchyma, which, in turn, was atelectatic, fibrous and occasionally contained discrete tubercles (figure 4).

The apex of the right lung was fibrous, and all three lobes contained discrete tubercles varying in size from 0.7 to 1.3 cm. The lower half of the upper lobe was gray, firm and solid and areas of caseous necrosis had developed.

Microscopical examination of the lungs showed typical tubercles with necrosis, giant and epitheloid cells, as well as lymphocytes and fibroblasts. The trachea had infiltrations of polyblasts, and tubercles were found in the submucous coat and adventitia. The bronchi of the right lung appeared normal. The left bronchus, except for occasional small areas of cartilage, mucous glands and muscle cells, consisted of chronic inflammatory and connective tissue. Tubercles, although rare, could be found in most of the sections examined. The bronchiectatic areas contained more normal tissue than the left main bronchus. Chronic inflammation was marked and typical tubercles were frequent.

Acid-fast microörganisms were found in the tissues of the trachea, left bronchus and bronchiectatic sacs.

Complete necropsy examination in three other cases revealed changes very similar to those described above. All showed mural obstruction, bronchiectasis, tubercles and acid-fast microörganisms.

FIG. 1. Case 1. Contraction of left lung. Displacement of heart and mediastinum to left. Pneumothorax with fluid level.

FIG. 2. Case 1. Obstruction of left stem-bronchus by a thin membrane completely occluding the bronchus.

FIG. 3. Case 1. Stenosis of the left stem-bronchus.

FIG. 4. Case 1. Extensive tuberculous bronchiectasis.

FIG. 5. Case 2. Tuberculosis of the right lung with numerous cavities. Localized tuberculosis of the left lung. Retraction of upper mediastinum and trachea to right.

FIG. 6. Case 2. Lipiodol injection. Bronchiectasis right. Two-stage thoracoplasty.

FIG. 1

FIG. 2

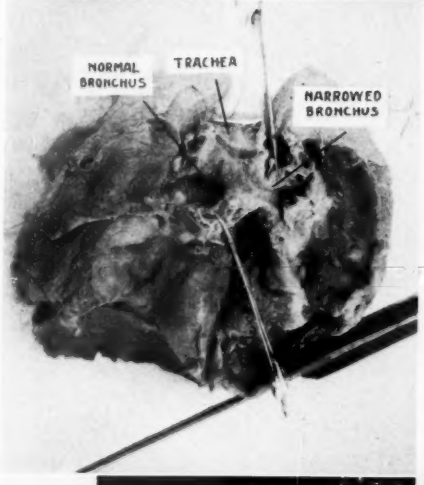


FIG. 3

FIG. 4

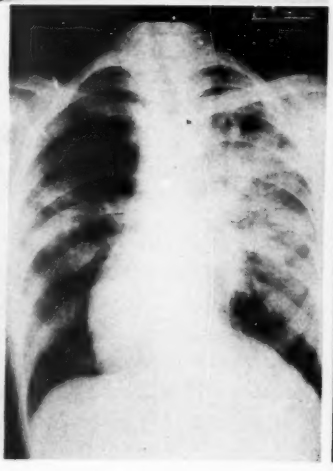


FIG. 5

FIG. 6

Case 2: F. M., a white woman, age 19 years, developed a persistent cough in May, 1930. She began to raise one ounce of mucopurulent sputum in June, 1930 and noted loss of weight, fever and weakness. The patient was admitted to Glen Lake Sanatorium on July 14, 1930, at which time tubercle bacilli were found in the sputum. Physical examination revealed dulness throughout the right lung with diminished breath-sounds. Coarse and moderately coarse râles were heard throughout. No abnormal physical findings were elicited on the left side. Roentgenological examination (figure 5) showed retraction of the upper mediastinum to the right as well as a fibroid and exudative type of tuberculosis involving the right lung from the apex to the fifth rib anteriorly with multiple cavities at the level of the first and second interspaces anteriorly. A similar process was present on the left side from the second to third interspace anteriorly with beginning cavitation.

Pneumothorax was instituted on the right side in 1931 and discontinued in 1933 because the collapse was considered unsatisfactory. Two stages of thoracoplasty were performed in 1933, with what appeared to be a satisfactory collapse. However, cough and expectoration up to 60 cc. daily persisted. No tubercle bacilli were found on direct examination but were found by guinea-pig inoculation. The patient was bronchoscoped in November, 1934, and the right main bronchus was found to be narrowed by tuberculous cicatricial tissue and granulations. Lipiodol studies showed extensive bronchiectasis on the right side (figure 6). Bronchoscopic examinations and treatments were frequently repeated (seven in all), and the condition showed no essential change except for a gradual increase in the degree of stenosis. Granulations were removed, 10 per cent silver nitrate was applied to the bronchial wall, and purulent secretion was aspirated each time. On the last bronchoscopic examination in September, 1936, the calibre of the right main bronchus, just below the bifurcation, was estimated at 3 mm. Slight improvement in the general condition resulted, but no permanent change in the amount of cough and expectoration was evident. The patient finally left the Sanatorium on November 15, 1936 in fair general condition, but continued to cough and raise up to 60 cc. of sputum daily.

This is a fairly typical history of pulmonary tuberculosis complicated by tuberculous bronchial obstruction and bronchiectasis. The complicating factors were not recognized until after an apparently successful thoracoplasty had been completed. This patient had no wheezing and no stridor.

Case 3: H. B., a single white woman, age 23 years, developed a persistent dry cough in the summer of 1930. In January, 1931 she had a haemoptysis (about 250 cc.), but she continued working until March, when her weakness and

cough became severe. She was admitted to Glen Lake Sanatorium in April, 1931. She was raising 4 to 6 cc. of mucopurulent sputum daily and tubercle

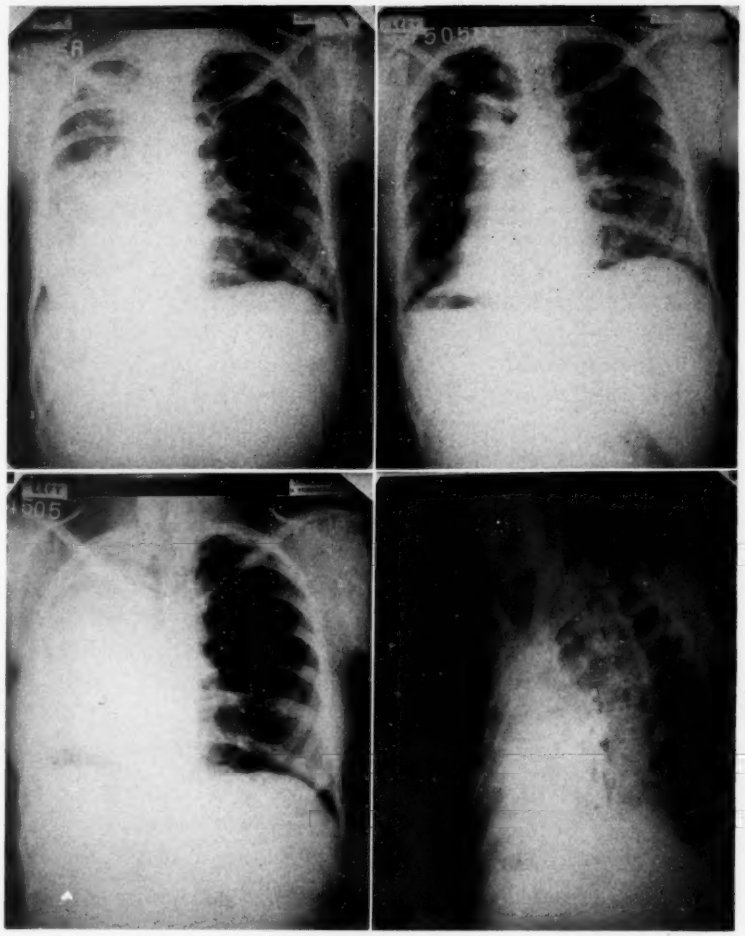


FIG. 7

FIG. 8

FIG. 9

FIG. 10

FIG. 7. Case 3. Tuberculosis of the left lung. Cavity in the left upper portion.

FIG. 8. Case 3. Pneumothorax left. (Increased expectoration despite good collapse.)

FIG. 9. Case 3. Reëxpansion of left lung with atelectasis. Stenosis of left stem-bronchus. Retraction of trachea, heart and mediastinum to the left.

FIG. 10. Case 3. Lipiodol injection. Five-stage thoracoplasty. Extensive fusiform bronchiectasis.

bacilli were found by smear. Physical examination of the right lung disclosed no abnormal findings. On the left side there was dulness throughout with almost complete absence of breath-sounds. Coarse râles were heard

posteriorly. Roentgenological examination (figure 7) revealed extensive pulmonary tuberculosis of the left lung with cavitation in the upper lobe. The pleura was thickened. The right lung appeared normal.

Pneumothorax was instituted on the left side in May, 1931, but, in spite of a satisfactory collapse (figure 8), the amount of expectoration increased to 20 cc. daily. Because an empyema developed, the left lung was allowed to reexpand in December, 1931. A definite atelectasis was present (figure 9) with retraction of the trachea and mediastinum toward the left side and elevation of the left diaphragm. Five stages of thoracoplasty were performed in 1932 and 1933. Prior to surgery the patient was expectorating 45 cc. of sputum daily. Instillation of lipiodol revealed a definite bronchiectasis in the left base. Even though the left lung was extensively collapsed by the thoracoplasty the patient now was raising up to 90 cc. of sputum daily. This amount was fairly constant through 1933 and 1934. No tubercle bacilli were found by direct examination. A left phreniphraxis, followed later by left phrenicectomy, had no appreciable effect. Her general condition was satisfactory except for a hypochromatic anaemia. She was discharged in May, 1934. Her symptoms remained unchanged until August, 1934, when she developed fever to 104°F., severe cough, blood-streaked sputum and marked toxaemia. This was, we believe, due to inadequate sputum drainage. She was readmitted to the Sanatorium and the acute attack subsided rapidly.

Bronchoscopic examination in August, 1934 revealed a stenosis of the left main bronchus. Blood-stained purulent secretion was aspirated and lipiodol introduced. Roentgenological examination revealed extensive bronchiectasis in the left lower lobe (figure 10). At the time of discharge, in December, 1934, she was raising 60 to 90 cc. of mucopurulent sputum daily. She has been seen frequently since, and at the present time (March, 1937) her sputum has increased to 120 to 180 cc. daily. The sputum is frequently blood-streaked.

The gradual increase in sputum suggests a progressive bronchiectasis. This occurred in spite of extensive surgical collapse. No tubercle bacilli have been found in the sputum since October, 1932.

Case 4: E. R., a white woman, 24 years of age, developed pleurisy on the right side in the summer of 1926. In April, 1927, she began to cough and expectorate and noted malaise with some loss of weight. A diagnosis of pulmonary tuberculosis was made, and she was admitted to Glen Lake Sanatorium in January, 1928. X-ray examination (figure 11) revealed a fine mottled diffuse infiltration throughout both lungs, more marked on the left, with a definite cavity in the left upper lobe and probably a cavity in the right apex. The sputum contained tubercle bacilli. Physical examination revealed moderately coarse râles throughout the left lung and some moderately coarse râles in the right upper lobe. Because permission for pneumothorax was refused, a left phreni-

phraxis was done in March, 1930 and a phrenicoexairesis a few months later. Permission for pneumothorax was finally obtained and established

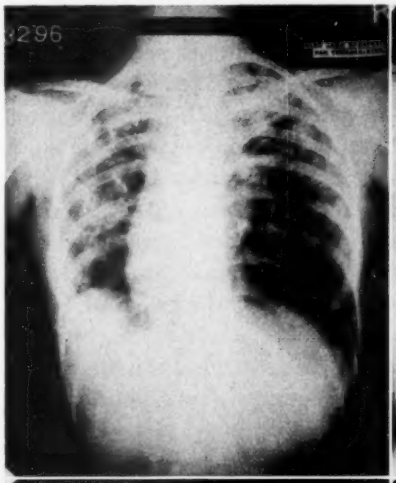


FIG. 11

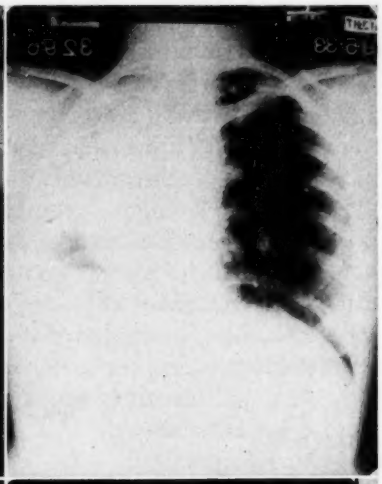


FIG. 12

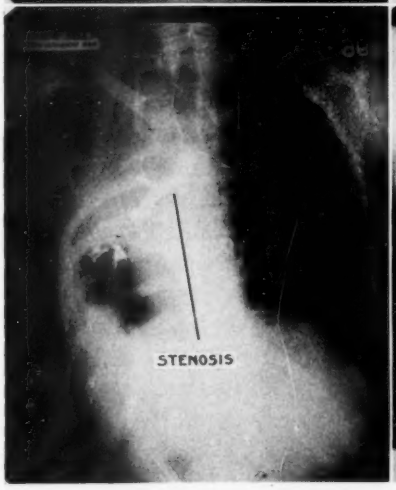


FIG. 13

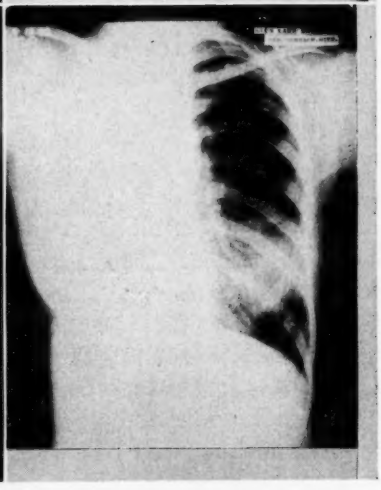


FIG. 14

FIG. 11. Case 4. Bilateral tuberculosis. Cavity in left upper lung field.

FIG. 12. Case 4. Contraction of left lung. High left diaphragm due to phrenicoexairesis and atelectasis. Retraction of mediastinum to left. Stenosis of left stem-bronchus.

FIG. 13. Case 4. Lipiodol injection. Stenosis of left bronchus. Bronchiectasis. Three-stage thoracoplasty.

FIG. 14. Case 5. Contracted right lung. Retraction of trachea, heart, mediastinum to the right. Cavity in right upper lung field, difficult to see.

in January, 1931, but was discontinued after seven months because the collapse was not satisfactory. In July, 1933, an atelectasis (figure 12) de-

veloped on the left side with further elevation of the diaphragm and retraction of the mediastinum to that side. Eventually three stages of thoracoplasty were performed with apparent closure of the cavity.

However, she continued to have cough and expectoration totalling 60 to 120 cc. daily. Frequent attacks of sputum retention were accompanied by excessive cough, fever to 103°F., severe toxaemia and dyspnoea. Lipiodol study (figure 13) revealed a definite narrowing of the left stem bronchus and bronchiectasis in the left base. After aspiration of several hundred cubic centimetres of purulent secretion through a bronchoscope the main bronchi were visualized. The right main bronchus was normal. The left main bronchus was filled with granulations producing a stenosis. She derived symptomatic benefit for several weeks but refused further bronchoscopic examination and treatment. She derived temporary benefit from frequent lipiodol instillations but continued to have severe toxaemia and distressing cough with expectoration of about 180 cc. daily. She left the Sanatorium in February, 1937 and died at home a few days later. Permission for necropsy examination was not obtained.

The bronchiectasis in this patient apparently developed following the atelectasis in 1933 and was due probably to the mural bronchial obstruction. We believe the obstruction and the bronchiectasis caused her death.

Case 5: M. O., a white woman, age 34 years, developed cough, expectoration, night sweats and malaise in 1930. These symptoms persisted for one year and recurred in the fall of 1932, but it was not until July, 1933, that a diagnosis of tuberculosis was made. She was admitted to Glen Lake Sanatorium in August, 1933. At this time she was raising about 60 cc. of sputum daily. Tubercle bacilli were present. On physical examination, the left lung was normal. On the right side there was dulness throughout, amphoric breath-sounds, whispered pectoriloquy and spoken bronchophony to the first interspace in front and the sixth dorsal spine posteriorly. The breath-sounds were absent in the lower lobe. A few fine râles were heard anteriorly below the third rib, and scattered coarse râles were heard posteriorly. Roentgenological examination (figure 14) showed an extensive pulmonary tuberculosis involving the entire right lung with cavitation in the upper lobe. A discrete fibroid tuberculosis was present in the left lung at the level of the second, third and fourth ribs anteriorly. There was marked displacement of the heart, aorta, and mediastinal structures to the right.

Pneumothorax, instituted soon after admission, was discontinued in January, 1935 because it was not satisfactory. Her general condition was poor with severe cough and expectoration up to 180 cc. daily. She ran a continuous

fever which not uncommonly rose to 105°F. and developed a severe secondary anaemia. A leucocytosis with high percentage of polymorphonuclears was present.

A marked obstruction of the right stem-bronchus, due to a cicatricial stenosis and granulations, was visualized by bronchoscopy in December, 1934. A large amount of bloody purulent secretion was aspirated. Monthly bronchoscopic examinations for the next year showed no essential change in the bronchial lesions. Following each bronchoscopy, there was a temporary improvement with decrease in fever, diminished cough and expectoration, increase in appetite, and some gain of weight. Lipiodol instillation revealed numerous large bronchiectatic cavities.

In April, 1936 the bronchiectatic abscesses were cauterized, a primary lobectomy being impossible because of dense pleural adhesions. In a short time her cough subsided, expectoration was reduced to 4 cc. daily, the temperature became normal, and her haemoglobin rose from 48 to 83 per cent (Sahli). Three stages of thoracoplasty closed the tuberculous cavitation in the upper lobe, and she still continues to raise about 4 cc. of sputum daily. No tubercle bacilli are found by direct examination.

In this patient, treatment for the bronchiectasis was carried out prior to the thoracoplasty with a satisfactory result, considering the poor general condition of the patient. This patient typifies one method of treatment which may be used, when the obstruction and the bronchiectasis are recognized prior to permanent collapse measures.

Case 6: M. N., a woman of 25, first complained of cough and weakness in 1931. Roentgenological examination at that time revealed tuberculosis. The patient refused treatment and continued to work until May 17, 1934, when she had a haemoptysis of about 250 cc. She was admitted to Glen Lake Sanatorium two weeks later. Physical examination revealed no abnormal pulmonary findings. Roentgenological examination (figure 15) showed a tuberculous fibroid infiltration involving the left lung from the third to fifth rib anteriorly. At this time there was no cough or expectoration. On strict bed-rest she improved at first, as shown by subsequent X-ray studies, but in January, 1935 she began to cough and expectorate sputum which contained tubercle bacilli. A spread of the tuberculous lesion was demonstrated, and pneumothorax was established on the left side. In spite of an apparently satisfactory collapse (figure 16), the patient continued to cough and expectorate up to 30 cc. daily. In addition, the patient noted loud noises in her chest and wheezing, often audible at a distance. Numerous rhonchi were heard in the left lung. An obstruction of the left main bronchus was demonstrated by lipiodol instillation, but no bronchiectasis could be shown. Bronchoscopic study in

August, 1935 revealed granulations of the left stem-bronchus causing partial obstruction. Bronchoscopy was repeated in April, 1936, and the bronchial

FIG. 15

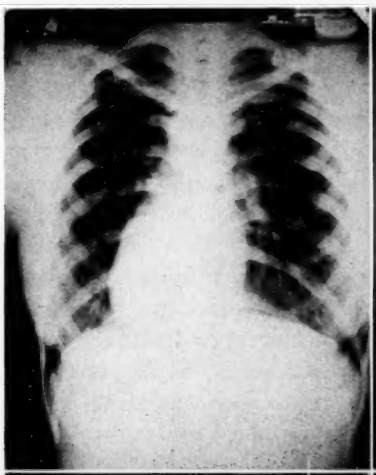
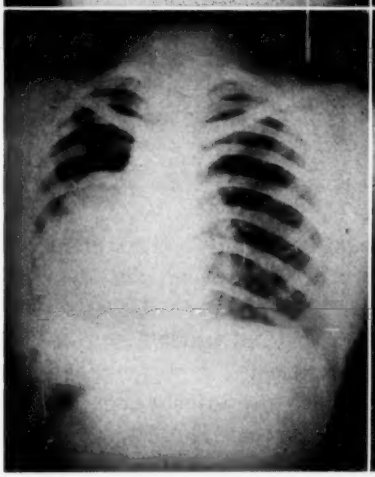


FIG. 16

FIG. 17



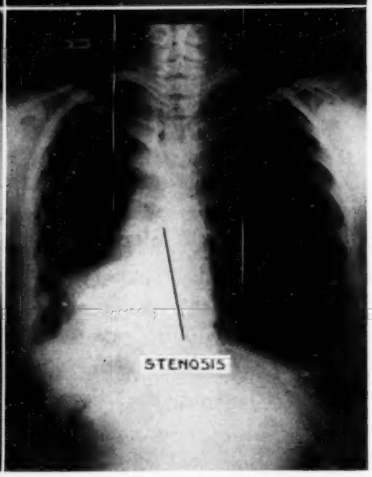


FIG. 18

FIG. 15. Case 6. Slight fibroid tuberculosis, third to fifth rib anteriorly, left.

FIG. 16. Case 6. Pneumothorax left. Stenosis of left main bronchus. (Continued cough, expectoration, wheezing.)

FIG. 17. Case 6. Pneumothorax left. Atelectasis following bronchoscopy. Temporary complete obstruction of left main bronchus.

FIG. 18. Case 6. Lipiodol injection. Stenosis of left main bronchus. Bronchiectasis in left basal portions.

lesion showed definite progression. A concentric stricture involving the left stem-bronchus just below the bifurcation was present. Following the bronchos-

copy, she developed increased cough and fever to 101°F. due to an atelectasis (figure 17) caused, we believe, by occlusion of the bronchial stricture as a result of the bronchoscopic manipulation and aspiration. Bronchoscopy, repeated in October, 1936, revealed similar findings. Following each bronchoscopy the wheezing, rhonchi, cough and expectoration temporarily disappeared. Pneumothorax has been continued to date. The patient, at the present time, is essentially unimproved and intermittently continues to cough, expectorate and wheeze.

Her general condition, so far, remains satisfactory. However, her sputum contains tubercle bacilli and her bronchiectasis will slowly progress. Lipiodol study, recently repeated, showed a definite bronchiectasis as well as the bronchial obstruction previously demonstrated (figure 18). Pneumonectomy is being considered for this patient.

This patient has been observed during the transition from a simple bronchial stenosis to one complicated by bronchiectasis. Even though the bronchial lesion in this patient was recognized early, control still remains difficult.

The preceding six patients demonstrate the development of bronchiectasis following pulmonary tuberculosis and tuberculous bronchial obstruction. As mentioned previously, we have studied, in addition, seven other cases with essentially similar findings. Four other patients have tuberculous bronchial obstruction with symptoms of bronchiectasis. Two patients have tuberculous bronchial stenosis without symptoms or findings of bronchiectasis.

SUMMARY AND CONCLUSIONS

1. Bronchiectasis, secondary to tuberculous bronchial obstruction, is not uncommon. Nineteen patients with tuberculous bronchial obstruction have been observed, and, in seventeen, signs or symptoms of bronchiectasis were present. The histories of six patients are given.

2. In our cases bronchial obstruction and infection of the bronchial wall were primary factors causing the bronchiectasis. Destruction of the bronchial mucosa and cilia, as well as atelectasis, may have been secondary factors.

3. Obstruction must be considered when wheezing, stridor and dyspnoea are present. Bronchiectasis should be suspected when the patient has unaccountable cough, expectoration, coarse râles or rhonchi.

4. The diagnosis may be confirmed by iodized oil and bronchoscopic examination. In addition bronchoscopy may be of value in local

treatment. No permanent harm has been demonstrated by these methods of diagnosis and treatment.

5. Collapse therapy, in the presence of obstruction and bronchiectasis, must be carefully evaluated to avoid disappointments. Treatment for the advanced bronchiectasis often must be undertaken before collapse of the tuberculous lesions will be successful.

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MASSIVE PULMONARY ATELECTASIS FOLLOWING BRONCHIAL OBSTRUCTION IN TUBERCULOSIS[1]

SAMUEL SANES AND WARREN S. SMITH

For the past decade, a world-wide interest has been focused on the recognition and study of that type of massive atelectasis which makes its appearance during the course of pulmonary tuberculosis.

REVIEW OF LITERATURE

A review of the literature indicates that the incidence of massive atelectasis in pulmonary tuberculosis is more frequent than its diagnosis. Perhaps the likelihood of its occurrence tends to be underestimated. In bleeding patients, its presence is sometimes overlooked because of the pardonable reluctance to submit such patients to the rigors of a complete physical and radiographic examination. That massive atelectasis at its acute onset in pulmonary tuberculosis can be mistaken for pleurisy with effusion, dilatation of the heart, coronary thrombosis, and pneumonia, not a few reports attest. More often it is confused, however, after the atelectatic lung has failed to reaerate itself and has become fibrotic, with chronic fibroid tuberculosis and chronic fibrous pleurisy with adhesions.

Total obstruction of a main bronchus to inspiration for a definite time comprises the essential aetiologic factor in practically all reported cases. Specific obstructing causes have been variously noted as (extrabronchial) enlarged lymph nodes and peribronchial fibrosis; and (intrabronchial) coagulated blood, fibrinous bronchial casts, caseous material, excessive secretion and obliterating bronchitis. Emphasis has also been placed upon factors which facilitate bronchial obstruction or weaken respiratory force, for example bronchial spasm, bronchitis, retained secretions, prolonged periods of rest in bed in supine position, immobilization of the chest by mechanical measures, and diminution of the cough reflex and respiratory rate by use of morphine.

The onset of massive atelectasis in pulmonary tuberculosis may be sudden or gradual. Not uncommonly the initial symptoms are mild

[1] From the Pathological Laboratory, Buffalo General Hospital, and University of Buffalo Medical School, Dr. K. Terplan, Director, Buffalo, New York.

or else obscured by the primary disease in the lung, and the atelectasis is discovered only accidentally upon physical or radiographic examination. The physical and radiographic findings closely resemble those of postoperative or posttraumatic collapse. Pendular movement of the heart is observed. Manometric readings show an increased negative pressure in the affected pleural cavity. As a consequence, artificial pneumothorax satisfactorily relieves the acute distress induced by mediastinal shift. In some cases bronchoscopy has confirmed the presence of bronchial obstruction and its cause. In intrabronchial obstruction complete recovery often follows spontaneous or operative evacuation of the blood clot, cast, etc. Pulmonary reinflation in cases with extrabronchial obstruction, for example enlarged nodes, is attributed to diminution in size of the compressing masses; here bronchoscopic dilatation has also been attempted. If bronchostenosis becomes permanent, diffuse fibrosis, of course, follows in the atelectatic lung. The mediastinal structures persist in displaced position; bronchiectasis usually supervenes. A beneficial effect on the course of tuberculosis in the affected lung is often noted.

In 1931 Hennell (1) analyzed the clinical and radiographic reports in a group of cases generally recognized up to that time as unusual types of chronic fibroid tuberculosis with adhesions, in which "the fibrosing process had kept pace with the activity of the ulcerating process." Hennell found these cases distinguished by a history of chronic cough, expectoration, extreme unilateral pulmonary fibrosis of many years duration, and displacement of the heart and mediastinum. Signs of toxaemia and activity such as fever, malaise, anaemia, leucocytosis, distinct loss of weight and bacilliferous sputum were strikingly absent. Correlating his findings with newly stressed data on the significance of atelectasis in pulmonary disease, Hennell made the brilliant deduction that, from a pathogenetic point of view, these cases of unilateral fibroid tuberculosis were not the results of a gradual ulceroproductive (or perhaps, diffuse pneumonic) inflammation but, in fact, instances of fibrotic lungs developing upon a massive atelectasis in which reaeration had not taken place.

During the past five years, further clinical material has been adduced in support of the view just summarized. Up to the present, however, no postmortem evidence, reported in detail in human beings, has appeared to substantiate Hennell's explanation. Consequently, the pathologic findings with proved aetiology in the following case of chronic massive atelectatic fibrosis in pulmonary tuberculosis, discovered inci-

dentally in a woman 37 years of age dying of lobar pneumonia, take on corroborative significance. For fourteen years, after the apparent onset of massive atelectasis, our patient presented a clinical and radiographic picture virtually identical with that described by Hennell.

CASE REPORT

H. H. (file no. 69750), 37 years of age, married, white, American, housewife, was admitted to the Buffalo General Hospital on the service of Dr. N. G. Russell, complaining of chills and severe pain in the left chest. She died within twenty-four hours.

The family history was irrelevant. As a child, the patient had suffered with measles, scarlet fever and whooping cough. In her late "teens" she left her rural home to seek work in the city. At the age of 23 years she became ill with acute respiratory symptoms. Examination as recalled by Dr. Thomas Walsh showed dulness over the right lower chest, and shifting of the heart toward the right. Paracentesis obtained no fluid. From this "chest condition" the patient never fully recovered. She continued to be harassed by frequent colds, cough, expectoration and pain in the right chest. Within four years the patient was admitted to J. N. Adam Memorial Hospital, Perrysburg, New York. Physical examination of the chest by Dr. Horace Lo Grasso showed poor nutrition, dulness at the right base, harsh bronchial breathing with few râles in the right upper half, and feeble breath-sounds over the right base. The left lung was not remarkable. During nine months' hospitalization the patient's temperature never varied from normal limits; her weight increased from 103 to 120 pounds; tubercle bacilli were never found in the sputum. Several attempts to aspirate the right chest procured no fluid. Roentgenograms showed dextrocardia and a homogeneous shadow of the entire right chest. No calcified nodes were visible. The discharge diagnosis was "moderately advanced pulmonary tuberculosis." It was felt, however, that the diagnosis had never been confirmed by laboratory findings.

Complaining of frequent "colds" the patient was next seen by Drs. Nelson G. Russell and Roy Scott, when she was 31 years old. Their findings included: temperature 98; pulse 80; blood-pressure 110/70; haemoglobin 80 per cent; white blood cell count 7,600; Wassermann, negative; sputum negative for tubercle bacilli; weight, 100 lbs. There was dulness and absent breath-sounds in the lower right chest and impaired resonance over the right upper lung field. A radiographic report by Dr. E. C. Koenig at this time read: Left chest: diffuse mottling throughout; thickening at hilum and large number of calcified nodes. Right chest: opaque from sixth rib to diaphragm. Heart drawn well to the right side. Several large calcified areas and numerous small calcified areas in upper part. Along the periphery there is a dark area of increased consistency. No fluid.

At the age of 34 years the patient was delivered by Dr. A. P. Walsh of a full-term male child. There was no difficulty. For the next three years the only complaints were "asthmatic" dyspnoea and cough.

Four days previous to her entry to the Buffalo General Hospital, the patient was suddenly seized with severe pain in the left chest, hacking cough, and intractable headache. *Physical examination* showed: temperature 105°F.; pulse 140; respiration 38; blood-pressure 90/80. Patient was thin, flushed, dyspnoeic. Labial herpes was present, cervical nodes were palpable. Right chest: Increased tactile fremitus in apex with bronchial breathing and râles. Absent fremitus, dulness, absent breath-sounds and vocal fremitus in remainder of chest. Left chest: Bronchial breathing throughout with râles and friction rub. The cardiac apical impulse was in the right fifth interspace; first sound, snappy and rough. In the abdomen no spasm, no masses. *Laboratory findings:* These included a pronounced polymorphonuclear leucocytosis. Sputum yielded type IV pneumococcus and no tubercle bacilli. Electrocardiogram showed nothing remarkable. *Radiographic findings* (figure 1) (Dr. E. C. Koenig): Right chest: heart and mediastinum to right; homogeneous density of right chest; no fluid level. Left chest: large density seen at periphery between fifth and seventh ribs. *Clinical course:* In the 24 hours following admission, the patient coughed incessantly and expectorated a mucoid pink sputum. Her cyanosis increased. Her terminal temperature was 104°F., her pulse was 150 and respirations 36.

Autopsy Report

The autopsy was performed five hours after death by Dr. K. Terplan and Dr. S. Sanes. The anatomical diagnosis was: *complete fibrous obstruction of the right main bronchus, practically throughout its whole course; complete calcification of right lower and upper tracheobronchial lymph nodes (following tuberculosis) lying along course of obstructed bronchus, marked atelectatic fibrosis and atrophy of whole right lung with pleuropericardial adhesions; multiple minute calcified areas in fibrosed right lung, dextroposition of heart; collapse deformity of right chest, compensatory emphysema and hypertrophy of left upper lobe; old tuberculous focus in apex of left upper lobe, a few small tuberculous nodules and calcified areas in left interlobar, bronchopulmonary and tracheobronchial lymph nodes; lobar pneumonia (pneumococcic) with fibrinous pleuritis of left lower lobe; a few gray tubercles in liver and left kidney; bilateral serous cystoma of ovaries; slight firm splenic tumor.*

The thoracic findings will be recounted in some detail. When the sternum was removed, only the left lung was seen. It reached beyond the midline apparently into the right pleural cavity. The right pleural cavity seemed at first glance to contain solely the heart and mediastinum. The pericardial sac was adherent to the chest wall and also to the medial surface of the left

upper lobe. Closer examination revealed in the upper portion of the right pleural cavity, chiefly in its most lateral part, a small, palm-sized firm mass.

FIG. 1

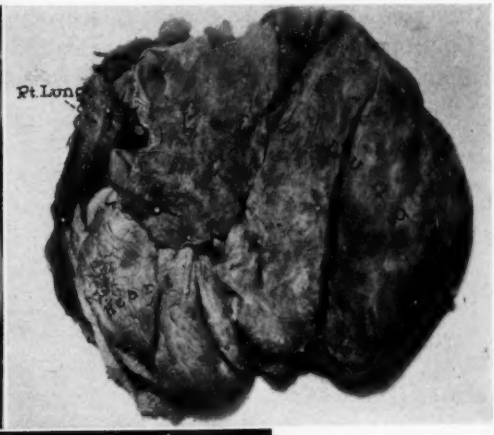

FIG. 2

FIG. 3

FIG. 1. X-ray film of chest showing homogeneous density of right chest; complete displacement of heart to right; and density in left chest between fifth and seventh ribs. (Taken several hours before death.)

FIG. 2. Anterior view of thoracic viscera showing hypertrophied pneumonic left lung; displaced heart to right; and atelectatic fibrosed right lung.

FIG. 3. Postmortem X-ray film of thoracic viscera, posterior view, showing hypertrophied pneumonic left lung; atelectatic fibrosed right lung with multiple calcified lesions; calcified right tracheobronchial lymph nodes; calcified foci in other lymph nodes; heart displaced to right.

Upon removal of the thoracic organs this mass was found to represent the right lung in a markedly atelectatic and fibrotic state. It measured 15 x 4 cm. Normal lobar markings could not be made out. (Figures 2 & 4.)

The trachea was patent, 4.2 cm. in circumference. The right bronchus was completely obstructed at a point several millimetres below the carina. A right inferior tracheobronchial lymph node, along the course of the bronchus, was almond-sized and apparently entirely calcified. A right upper tracheobronchial node was date-sized and entirely calcified. Other lymph nodes in these groups were also calcified. The right lung was adherent medially to adjacent nodes. Gross serial sections through the right bronchus, nodes and

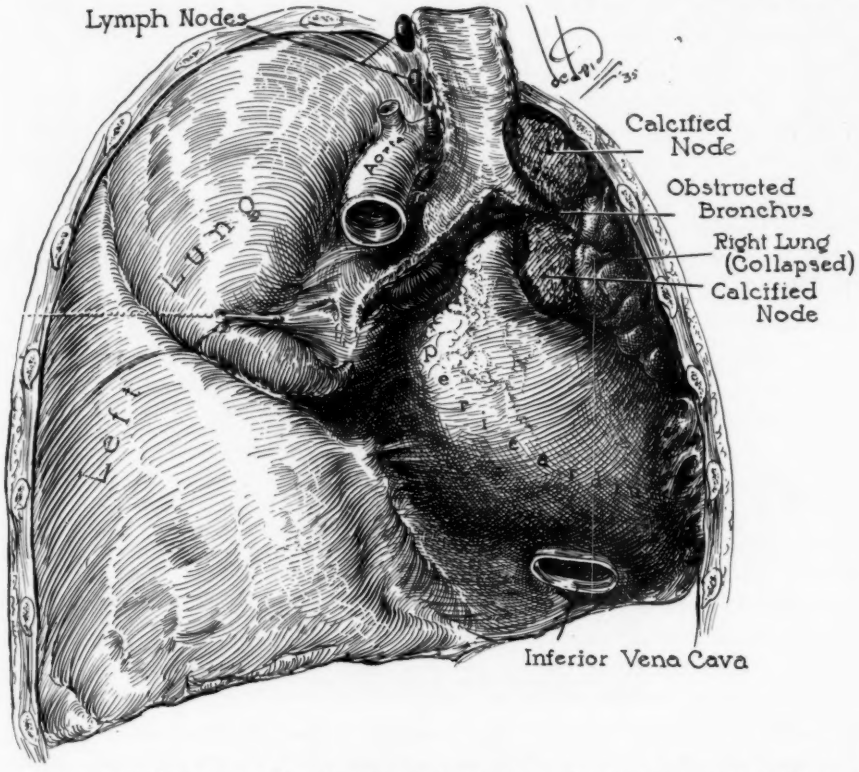

FIG. 4. Posterior view of thoracic viscera showing hypertrophied pneumonic left lung; atelectatic fibrosed right lung; obstructed right bronchus; and calcified right tracheobronchial lymph nodes. (Diagrammatic representation.)

lung showed complete obstruction of the bronchus in intimate connection with calcified tracheobronchial lymph nodes and calcified foci in the fibrotic pulmonary parenchyma.

The left main bronchus measured 7.5 cm. in length and 3.2 cm. in circumference. It was patent throughout its entire course. The left lung was voluminous especially in the upper lobe, which showed a deep indentation in its basal part at its inferior surface, that formed almost three lobes. The apex

of the left lung revealed a hazel-nut-sized anthracotic, fibrous focus with a few small tubercles and a few bronchiectatic cavities. The lower lobe showed a typical lobar pneumonia with fibrinous pleuritis. A few gray band-like adhesions were also present between visceral and parietal pleurae. In the left bronchopulmonary and interlobar lymph nodes were a few small tubercles and pea-sized calcified foci. The left lower tracheobronchial nodes were bean-sized and on section showed a few small gray tubercles.

X-ray films of the lungs with the heart attached, made postmortem (figure 3), confirmed and amplified the gross findings as far as calcified lesions were concerned. In the atelectatic and carnified lung were multiple calcified spots. Besides the extensive calcification in the right upper and lower tracheobronchial group, one right lower tracheobronchial node contained a small calcified area. Calcified lesions were demonstrated in the left lung, and left interlobar, bronchopulmonary, tracheobronchial and paratracheal nodes.

The *histologic findings* can be summarized thus: The large lymph node along the course of the right main bronchus showed a markedly thickened capsule which was composed of dense, hyalin fibrous tissue. The fibrous tissue was arranged in collagenous bands which ran parallel to each other. Very few cells were seen; the nuclei were dark, flat and elongated. The normal lymphatic structure within the node had for the most part disappeared. Only in the centre and in astral bands radiating from the centre were lymph follicles and lymphocytes obscurely noted. Between the bands and in the centre was much chalky material. In the periphery of the node there was distinct calcification. The inner border of the capsule was indented by calcified masses and showed a scalloped appearance. Other small calcified masses were included in compartments surrounded by fibrous bands. No tubercles were seen. There was no bone formation. In other lymph nodes the structure was better preserved. These nodes contained chalky calcific nodules and revealed fibrosis.

Surrounding the huge chalky and calcified node was fibrous and fatty tissue. The lymph node capsule could be followed with good differentiation. However, laterally, especially in one section examined, the capsule of the lymph node blended with the outer layer of the bronchus. The medial cartilages of the main bronchus were displaced inward. The outer layer of the bronchus was thickened. At one point, the site of focal collections of lymphocytes, thickened vessels and nerves, the impression was gained that the outer fibres of the lymph node capsule passed inward between cartilages into the bronchus.

Except for the presence of cartilages, normal internal layers of the bronchus could not be made out. The lumen was completely obliterated. It was filled with hyalin fibrous tissue. In places the fibrous tissue was dense and closely packed. In many areas the fibrous strands were separated by spaces which possessed no definite lining. Bands which circumscribed these spaces were

incrusted with black pigment. Scattered throughout were small capillaries; most of these were devoid of blood. The cartilages, especially at their ends, showed ossification. In one area, apparently corresponding to the submucous layer of the bronchus, a few small gland-like structures were seen. In these structures, a basement membrane was noted. On this membrane were situated cells, moderate in size, with pink cytoplasm, oval, dark nuclei and ob-

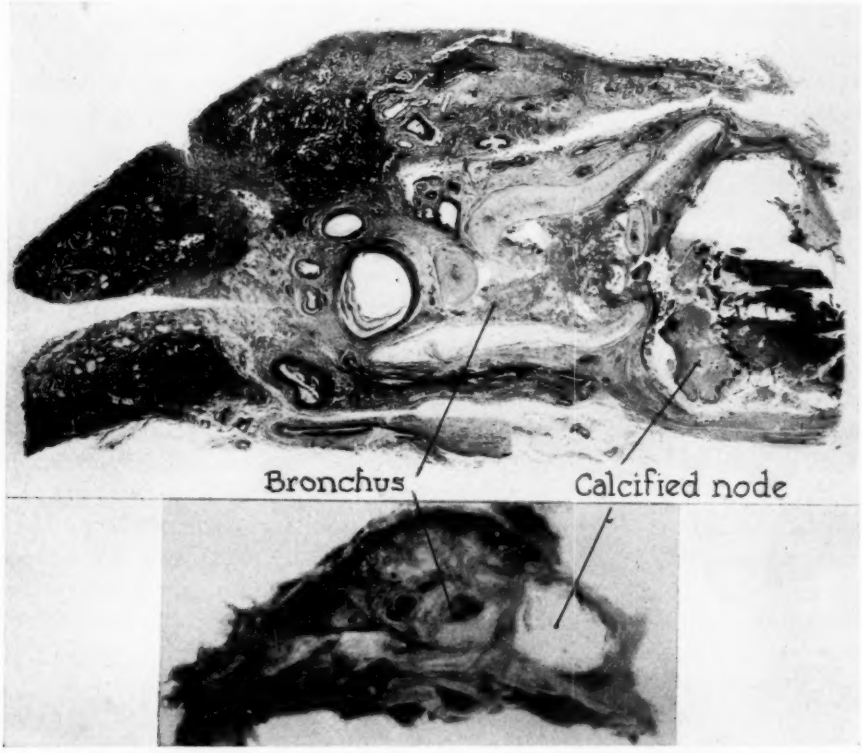

FIG. 5. Gross and corresponding histological section showing calcified tracheobronchial lymph node along obliterated right main bronchus; and atelectatic fibrosed right lung. (Microsummar.)

scure outlines. In close proximity to the gland-like structures were collections of lymphocytes. Second-order bronchi were also obliterated.

In the lung itself obvious alveolar structures no longer remained. The periphery of the lung consisted of compact fibrous tissue with few nuclei; there were many moderately sized vessels which contained no blood. In places, one observed spaces lined and filled by oval cells with dark nuclei and a slight amount of pink cytoplasm. In the midsuperior position, structures resembling collapsed alveoli were present. These comprised spaces lined by

flat cells; their walls were slightly thickened. Distributed among the spaces were patent tubes which appeared like persistent bronchioles. On a basement membrane rested columnar cells with basal nuclei and pink-staining free borders. Cartilages were not present. Elastic tissue could be demonstrated in the walls of spaces and in fibrosed parts of the lung. Scattered throughout the lung were chalky calcified foci with thick fibrous capsules; in the periphery of some of these foci, bone formation had taken place. The vessels in the collapsed and fibrosed lung were thickened.

COMMENT

In the case here reported, the terminal symptoms of acute pain, cough, fever, left pulmonic consolidation and leucocytosis can be entirely related to the primary cause of death—lobar pneumonia of the left lung. For fourteen years, however, before her fatal illness, the patient presented a clinical and radiographic picture which was as intriguing as it was constant. Following an acute attack of dyspnoea and pain in the right chest, she developed chronic cough, expectoration and "asthmatic" breathing. Physical examination of the left chest revealed nothing remarkable; at one time roentgenograms showed diffuse mottling, thickening at the hilum and calcified nodes. The right chest, on the other hand, presented collapse deformity, impaired resonance and bronchial breathing in the upper third, dulness, absent breath-sounds and vocal fremitus in the lower portion; X-ray films depicted diffuse homogeneous density. The heart was completely displaced to the right.

Despite the manifest and persistent findings in the right chest which evoked on several occasions the diagnosis of fibroid pulmonary tuberculosis, measurable evidence "of tuberculous infection or toxaemia" was lacking. There was no fever, leucocytosis, distinct loss of weight or positive sputum; anaemia was slight. Repeated pleural punctures failed to obtain fluid. From the history, pneumonia, pneumothorax and empyema could be ruled out with safety. Indeed, for all her adult life, our patient possessed those complaints and radiographic features which Hennell (1) (and after him others) designated as characterizing certain cases of extensive unilateral fibroid tuberculosis in which the fibrosis, according to his clinical speculation, was dependent upon persistent pulmonary atelectasis due to bronchial obstruction rather than, as had been commonly believed, upon a gradual ulceroproductive or diffuse pneumonic tuberculous inflammation.

Our autopsy studies disclosed, in addition to a lobar pneumonia and

old tuberculous lesions in the left lung, chronic fibrosis of the right lung pursuant to massive atelectasis. The atelectasis was associated with a complete fibrous obliteration of the right main bronchus and its branches, which in turn was associated with chalky calcific changes in tracheobronchial nodes following tuberculous lymphadenitis and perilymphadenitis. It would appear, then, that in our case we are able to offer the first completely described postmortem basis for the validity of Hennell's conception of the pathogenetic rôle of massive atelectasis in certain instances of unilateral fibroid tuberculosis.

Our findings further bear importance when viewed in regard to discussions on the mode of production of bronchial occlusion in massive fibrosed atelectasis in adults. In such discussions two questions have usually arisen. First, does bronchial obstruction occur most frequently from a lesion within or from a lesion outside the respiratory tube? Secondly, does the atelectasis result from multiple stenoses of small bronchi or from closure of a major bronchus? Pagel and Henke (2), Eloesser (3), and Westermark (4) present evidence which points to the intrabronchial or mural mode of obstruction. Ranke, Arnstein (5), Eloesser (3), Fleischner (6), and Reichle and Frost (7) note how obliterating bronchitis may follow a spread of tuberculous infection from external nodes. Eloesser also shows how bronchial compression and deformity may result because of involvement of contiguous nodes. As to the second question, Stivelman (8) (excluding cases in children) states that no reliable evidence has ever been offered which could be used to decide whether massive fibrosed atelectasis in pulmonary tuberculosis depends on old primary plugging of a main bronchus or whether it is actually "a multilobular atelectasis which has slowly progressed so as ultimately to involve the larger and main bronchi."

We must admit that in our case we are studying a pathological end stage. Nevertheless on the basis of the clinical, radiographic and postmortem findings, observed from inception through a period of fourteen years, we feel somewhat justified to conjecture on the type of bronchial obstruction and on the manner of the development of massive fibrosed atelectasis. First the patient suffered from tuberculous lymphadenitis and perilymphadenitis in the right tracheobronchial group. Infection spread into the right main bronchus and brought about obturation. (Perhaps there was also some compression.) Acute massive atelectasis ensued. When the right lung failed to reaerate itself, because the bronchitis progressed and proceeded to chronic obstruction, atelectasis

was gradually converted into collapse-induration. Early, the lymph nodes of the mediastinum were not visible in X-ray films; later, roentgenological studies indicated the presence of calcification. Is it permissible, then, to consider that in our case massive fibrosed atelectasis resulted from obliteration of a major bronchus and that the infection, fundamentally responsible, originated from without the bronchus?

Finally, from the gross and histological findings it also appears reasonable to assume that in our case the tuberculous lymphadenitis which initiated the massive atelectasis was part of a complex which characterizes the primary type of infection and that this lymphadenitis manifested itself in early adult life. The clinical and pathological literature (9) contains sporadic examples of massive atelectasis in children connected with primary complex formation. Sproull (10) went so far as to suspect, on the basis of reported observations in children and from his own clinical and radiographic experience, the occurrence of bronchial obstruction by tuberculous nodes with massive atelectasis in adults, but feared to predicate this pathogenetic supposition because of the lack of confirmatory pathological reports in adults. Eloesser has described bronchial stenosis due to tuberculous nodes with bronchoscopic, operative and biopsy evidence. In the past few years tuberculin surveys and postmortem studies have established the fact that the incidence of primary tuberculous infection in children has greatly diminished. In certain parts of the United States only 10 to 30 per cent of children up to 15 years of age give positive tuberculin reactions. In carefully examined autopsies on white children, aged 1 month to 18 years, Terplan (11) found tuberculous lesions in about 20 to 25 per cent. An increased frequency of primary tuberculosis in adolescence and adult life looms as a probability. Terplan had a small number of white persons between 20 and 40 years who showed no Ghon foci at autopsy. He also demonstrated anatomically recent complexes in adults. In persons with completely healed primary complexes and negative tuberculin tests, the possibility that secondary tuberculous infection may assume the form of a primary lesion must be considered. Our case lends factual strength to the clinical suspicion, held, for example, by Sproull (10), that one can be dealing in adults with cases of obstructive massive atelectasis associated not only with tuberculous lymph nodes but with lymph nodes in complex changes of the primary type.

The transliteration of the effects of massive atelectasis in pulmonary tuberculosis into terms of obstruction of small bronchi and partial

atelectasis in an already diseased lung may throw a new light upon the evolution of fibroid changes in cases with rather sudden appearance of physical signs and X-ray findings. Rapid fibrosis with retraction of interspaces and deviation of the trachea, which cannot satisfactorily be explained by gradual tuberculous infiltration, becomes clear when the underlying change is considered identical to that in massive atelectasis, only in epitomized form. Adams and Livingston (12) found that in dogs with gradually induced bronchial stenosis lobular obstruction is not followed by atelectasis of the obstructed part. Coryllos (13) points out that cavities heal by collapse consequent to bronchial obstruction.

SUMMARY

A brief abstract of the available literature on massive pulmonary atelectasis (collapse) following bronchial obstruction in tuberculosis is made. The clinical, radiographic and postmortem findings, studied in a 37 year old woman for fourteen years from inception, of massive atelectatic fibrosis of the right lung following obliterating bronchitis associated with tuberculous lymphadenitis and perilymphadenitis of tracheobronchial lymph nodes are reported. The significance of these findings in relation to the pathogenesis of bronchial obstruction, massive atelectasis and certain forms of fibroid changes in pulmonary tuberculosis is pointed out.

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RADIOLOGICAL MEASUREMENTS OF THE RESPIRATORY MOTION OF THE PNEUMOTHORAX LUNG[1]

ANDREW L. BANYAI

According to a generally accepted conception the low-tension type of artificial pneumothorax puts the lung at rest. Contrary to this, Korol (1) quotes Olmer and Raybaud who, while making kymographic tracings of the chest-wall and of the collapsed lung, found that vigorous intrapleural movements may be present after the movements of the chest-wall have become too feeble to register on the kymograph. Schnippenkoetter (2) and Cutler (3) observed during fluoroscopic examination that the pneumothorax lung makes large respiratory excursions. Schnippenkoetter (2) emphasized that collapse by artificial pneumothorax and rest are not synonymous. Fleischner (4) reports that in artificial pneumothorax the uninvolved part of the treated lung is more collapsed and moves less than the diseased part after the first inflation; the converse condition is noticeable in a few days, after the second or third inflations. His observation that the greater the collapse the less is the motion of the treated lung, is in harmony with the teaching of Liebermeister (5) that the capillary cohesion between the walls of the air cells and the bronchioles of the collapsed lung hinders or counteracts the effect of traction exerted by inspiration. Alexander (6) noted that the lung is not put at rest by artificial pneumothorax. Brieger (7) states that the collapsed lung participates normally in the respiratory function. The extensive experimental studies of Torning (8) brought out valuable data in this respect. In rabbits with unilateral artificial pneumothorax, the relation between the ventilation of two sides is generally unaltered by the insufflation into one pleural cavity of a volume of air equal to or greater than the volume of one lung. The depth of respiration of the individual lung is but little affected by slight degrees of collapse. Even with a pneumothorax of a size approaching the double of the total volume of the two lungs the pneumothorax lung is far from ceasing to function altogether.

On the basis of his clinical observations, Wiesinger (9) refutes the postulate that immobilization of the lung is a curative factor in artificial

[1] From the Muirdale Sanatorium, Wauwatosa, Wisconsin.

pneumothorax. The benefits of this treatment are attributed by him to collapse and to the stagnation of blood and lymph. Korol (1) says that there is an increased respiratory activity of the collapsed lung in all cases of artificial pneumothorax. Frola and Bianchi (10), on the other hand, found that, although the collapsed lung shows, at times, definite respiratory motions, the pulmonary motions are in some cases caused only by the pendulum motion of the mediastinum. According to Warembourg (11), in selective pneumothorax the healthy lobes expand more than usual to fill the thoracic cavity and their respiratory motion is marked if the pleura is free, while the diseased lung collapses and only passively follows the motion of the surrounding organs. Chersi (12) is of the opinion that the occasional rapid and surprising effect of an early pneumothorax is induced by a hyperaemia that is brought about by an increased inspiratory and decreased expiratory activity following artificial pneumothorax. Menozzi (13) differentiates two types of collapse: (*1*) hyperkinetic collapse: this is due to increased vagotonus; the difference between the initial and final manometer reading is small, the pneumothorax space is not wide, the lung tissue is light on the roentgenogram, except the tuberculous area, and the lung participates considerably in the respiratory motions; (*2*) paralytic collapse, that is, hypotony of the vagus: the circulation is almost abolished, the lung field is hazy on the roentgenogram, and there is no motion of the lung even on deep inspiration. The studies of Reichel (14) revealed that, although the collapsed lung has respiratory motion, this is slight on quiet respiration. The opinion of Bock (15) occupies a middle position between the two extremes; according to him it is possible that artificial pneumothorax may cause a change in the ventilation in some parts of the lung and thus it may rest the diseased part; the absence of rest of the collapsed lung does not exclude the rest of some of its parts.

We have studied the motion of the pneumothorax lung in 52 individual cases. Of these, 42 had unilateral and 10 bilateral pneumothorax; thus 62 pneumothorax lungs were measured. For comparison, the respiratory motions of the normal lung and thorax were studied in 47 healthy adults. Altogether 109 radiological respiratory ratios were analyzed. The measurements were made on roentgenograms according to a method described by Hurtado and Fray (16) that was devised for the determination of the respiratory expansion of the chest. They found that the degree of chest expansion can be estimated from the relationship between the areas of the roentgenological lung fields at maximum expiration and

inspiration. The roentgenograms used in our work were taken at the end of the two respiratory phases, in the upright position, on two films, at a distance of six feet. The margin of the collapsed lung was outlined and the pulmonary area measured by means of a planimeter. The figures on the differential wheel of the planimeter used by us indicate areas in square centimetres. When measuring the area of the noncollapsed lung or of one-half of the thorax the tracer arm of the planimeter was moved along the inner aspect of the ribs from the midline to the diaphragm, encircling the lateral margin of the lung, from the costophrenic angle over the dome of the diaphragm to the midline, and from here along the midline to the apex.

The radiological respiratory ratio was calculated according to the following formula: radiological area at maximum expiration over radiological area at maximum inspiration times 100. This ratio is inversely proportionate to the extent of respiratory excursion. The radiological respiratory ratio of the pneumothorax lung varied from 54 to 99, that is, in some cases motion of the collapsed lung persisted in such a degree that the radiological inspiratory area was almost twice as large as the radiological expiratory area, while at the other extreme the respiratory motions of the collapsed lung were practically absent. The extent of respiratory motion is reflected by the following grouping: radiological respiratory ratio between 50 and 59, 11; 60 and 69, 20; 70 and 79, 17; 80 and 89, 11; and 90 and 99, 3 cases. The last group represents cases with very slight motion. Two of these three patients were studied following their first artificial-pneumothorax treatment. It may be thought that this fact might explain the limited motion of the collapsed lung as contrasted with patients in whom the observations were made on a well established pneumothorax. Against such an assumption speaks the fact that there were two patients with initial pneumothorax in whom the respiratory ratios were between 54 and 69. On the other hand, it should be observed that, while there were only two instances of initial treatment between the ratios of 54 and 69 in 31 observations, the number of initial treatment cases was seven in the groups with respiratory ratios between 70 and 99, also in 31 observations.

As to the influence of band-like adhesions, and the lack of free apical separation, we found these conditions less frequently in patients with marked pulmonary motion, although it was often the case that vigorous pulmonary motion existed in the presence of single or multiple thin apical or subapical band-like adhesions. Outside of the initial treatment cases,

there seemed to be no relationship between the radiological respiratory ratio and the duration of pneumothorax treatment. The longest treatment was two years and eight and one-half months. The respiratory ratio in this case (serial number 41R) was 76.

A study of the intrapleural pressure before and after inflation revealed that variations in the intrapleural pressure, as recorded in our cases, had no bearing upon the respiratory excursions of the collapsed lung, so long as the pressure was kept on the negative side. The manometer readings represent the oscillations of the water in both legs of the manometer (true readings). The initial manometer readings were between −17 and −4, the final readings between −10 and −2, except in one instance (case 6) in which it was 0.

No parallelism was found between the amount of injected air and the radiological respiratory ratio. In other words, the amount of injected air, as long as the intrapleural pressure is kept on the negative side, does not influence the respiratory motion of the collapsed lung. Marked, moderate and slight respiratory excursions were seen following the administration of 500 to 600 cc. of air as well as that of smaller amounts. The majority of our cases received 500 cc. or more. The injected air was less than 300 cc. in three instances.

An attempt was made to determine whether there is any relationship between the degree of pulmonary deflation, produced by artificial pneumothorax, and the radiological respiratory ratio. The degree of deflation was calculated according to the following formula: radiological area of collapsed lung at maximum expiration over radiological area of the homolateral thorax at maximum expiration times 100. The degree of deflation varied from 30 to 95. There were 6 cases between 30 and 39, 4 between 40 and 49, 10 between 50 and 59, 9 between 60 and 69, 18 between 70 and 79, 12 between 80 and 89, 2 between 90 and 95, and the measurements were incomplete in one instance. A review of table 2 reveals that the degree of deflation of the pneumothorax lung is not a reliable determining factor of its respiratory excursion. Marked as well as limited respiratory mobility was observed in cases with marked degree of deflation. Cases with a deflation ratio of 80 or more showed less respiratory motion of the treated lung, than cases with a deflation ratio below 80.

The influence of the motion of the chest-wall upon the motion of the pneumothorax lung was discussed by Pinner (17) who says that the respiratory motions of the lung are solely activated by the motion of

TABLE 1

Cases arranged according to the radiological respiratory ratios of the pneumothorax lung

SERIAL NUMBER	RADIOLOGICAL RESPIRATORY RATIO		INTRAPLEURAL PRESSURE		AMOUNT OF AIR INJECTED	AGE	DURATION OF		REMARKS
	Pneumothorax lung	Overlying thorax	Initial	Final			Pneumothorax	Disease	
					cc.	*years*			
20	54	80	−9	−8	600	17	2 m.	5 m.	Thin adhesions
3	55	68	−13	−6	600	19	18 m.	2 y. 4 m.	No apical separation
17L	55	78	−7	−7	500	26	2½ m.	3 y. 8 m.	Bilateral pneumothorax. Thin adhesion
45	55	71	−11	−7	600	13	3 w.	2 y.	
1	56	76	−10	−6	600	18	5½ m.	1 y. 2 m.	
21	57	75	−15	−10	400	23	1 y. 6 m.	6 y. 6 m.	Small effusion
35	57	78	−12	−6	500	33	11 m.	1 y. 4 m.	Thin adhesions. Small effusion
47	57	65	−12	−8	300	15	F	2 m.	
26	58	92	−8	−3	250	26	8½ m.	1 y. 4 m.	No apical separation. Effusion
7	59	83	−6	−5	350	30	1 y. 4 m.	2 y. 2 m.	Multiple thin adhesions
25	59	77	−8	−4	500	29	1 w.	5 m.	Multiple adhesions
13	60	79	−10	−5	400	18	3 w.	4 y.	Bilateral pneumothorax
28L	60	73	−17	−10	350	24	3 w.	4 m.	Multiple adhesions
38R	60	91	−8	−4	300	18	1 y. 7 m.	2 y. 6 m.	Bilateral pneumothorax. Small effusion
14	61	—	−5	−4	350	17	1 m.	2 m.	
36	61	67	−14	−6	500	36	1 m.	8 y.	
49	61	90	−12	−3	400	28	3 m.	6 m.	Multiple thin adhesions
30	62	86	−9	−4	500	15	2 w.	4 m.	Lower lobe lesion
34	65	92	−9	−2	300	14	9 m.	Not known	Thin adhesions
52	65	74	−8	−4	500	37	1 w.	1¼ m.	Multiple thin adhesions
10R	66	73	−12	−7	500	28	2 m.	1 y. 4 m.	Bilateral pneumothorax
2R	66	79	−4	−3	500	25	1 y. 5 m.	3 y. 5 m.	Bilateral pneumothorax

32	66	76	−10	−5	500	30	2 w.	3 y.	No apical separation. Adhesion
38L	66	88	−8	−4	300	18	1 y. 7 m.	2 y. 6 m.	Bilateral pneumothorax. No apical separation
16	67	74	−10	−5	250	23	1 m.	2 y. 10 m.	
28R	67	67	−11	−7	500	24	1 m.	4 m.	Bilateral pneumothorax. Multiple adhesions
41L	67	78	−11	−4	400	41	2 y. 7 m.	8 y.	Bilateral pneumothorax. Apical adhesions
22L	68	74	−9	−9	400	28	1½ m.	8 m.	Bilateral pneumothorax. Thin apical adhesion
18	69	82	−10	−8	600	26	2 m.	6 m.	
31	69	86	−9	−5	500	15	3 w.	7 m.	Multiple apical adhesions
51R	69	82	−8	−8	300	27	F	10 m.	Bilateral pneumothorax. Small effusion
39	71	80	−14	−6	500	26	1 m.	2 m.	Thin apical adhesions
46	71	78	−8	−5	300	19	F	6 w.	No apical separation
8	72	85	−13	−6	600	24	2 w.	4 m.	Apical subapical adhesions
9	72	84	−9	−5	600	23	1 m.	1 y. 11 m.	No apical separation
22R	72	82	−7	−5	500	28	1½ m.	8 m.	Bilateral pneumothorax. No apical separation
24	72	85	−11	−6	500	30	1 w.	3 m.	Multiple, thin, lateral adhesions
10L	73	76	−12	−9	400	28	2 m.	1 y. 4 m.	Bilateral pneumothorax. Multiple adhesions
37	73	78	−10	−6	500	23	1 m.	7 m.	Basal lesion. Subapical adhesion
42	75	87	−6	−2	500	24	8½ m.	1 y. 1 m.	Thin, apical adhesions
2L	76	81	−5	−3	300	25	1 y. 5 m.	3 y. 5 m.	Bilateral pneumothorax. No apical separation
41R	76	96	−10	−8	400	41	2 y. 8 m.	8 y.	Bilateral pneumothorax. Apical adhesion
12	78	86	−8	−6	350	31	4 days	7 y.	Apical adhesion
19L	78	92	−11	−10	600	26	1½ m.	1 y. 3 m.	Bilateral pneumothorax. Thin, apical adhesion
48R	78	90	−10	−4	400	26	4 m.	2 y.	Bilateral pneumothorax. Thin, apical adhesion
19R	79	81	−10	−11	500	26	1½ m.	1 y. 3 m.	Bilateral pneumothorax. No apical separation
43	79	87	−10	−5	500	20	3 w.	1 y. 7 m.	No apical separation
51L	79	87	−8	−6	300	27	F	10 m.	Bilateral pneumothorax
17R	81	90	−11	−8	450	19	18 m.	2 y. 4 m.	Bilateral pneumothorax
27	81	88	−10	−6	500	22	1 m.	11 m.	Multiple thin adhesions
44	81	94	−6	−5	600	23	1 y. 4 m.	1 y. 9 m.	Multiple thin adhesions
50	81	93	−12	−8	500	19	F	1 y.	Thin, apical adhesion

Abbreviations: F = First Treatment; R = Right; L = Left; M = Month; W = Weeks; Y = Years

TABLE 1—*Concluded*

SERIAL NUMBER	RADIOLOGICAL RESPIRATORY RATIO		INTRAPLEURAL PRESSURE		AMOUNT OF AIR INJECTED	AGE	DURATION OF		REMARKS
	Pneumothorax lung	Overlying thorax	Initial	Final			Pneumothorax	Disease	
					cc.	*years*			
5	82	86	−13	−6	500	52	F	1 y. 4 m.	
4	83	85	−10	−8	500	17	F	4 m.	No apical separation
11	84	93	−7	−3	500	46	5 m.	1 y. 9 m.	Multiple adhesions. Small effusion
33	84	98	−16	−8	500	46	1 y. 9 m.	2 y. 8 m.	Wide, subapical adhesion
40	84	89	−10	−2	200	28	4½ m.	1 y. 6 m.	Wide, apical adhesion
48L	87	92	−10	−4	400	26	6 m.	2 y.	Bilateral pneumothorax. Thin apical adhesion
23	89	90	−6	−3	600	29	2 m.	3 m.	Multiple, thin adhesions
29	95	96	−7	−6	350	56	F	4 m.	Wide, apical adhesions
6	99	97	−6	−0	150	29	F	4 m.	
15	99	99	−22	−6	300	46	1 m.	2 y.	No apical separation

the chest-wall (including the diaphragm). This is equally true for a normally expanded as well as for a collapsed lung. Furthermore, he says, that even a large pneumothorax cannot alter the dependence of pulmonary motion upon thoracic motion up to the point where the intrapleural pressure is atmospheric or positive during the entire respiratory cycle. Korol (1) concluded from his observations that, while under normal conditions the movements of the lung are limited in extent by the activity of the overlying chest-wall, if the lung is separated from the chest-wall by a layer of gas, as in artificial pneumothorax, the force of the movements of the chest-wall is exerted evenly on the entire lung, in accordance with the law of Pascal, and the collapsed lung, functioning without residual air, shows greater respiratory excursions than the overlying chest-wall.

Our measurements of the radiological area of the collapsed lung and of the overlying thorax afford us a practical means for estimating the effect of the motion of the chest-wall upon the collapsed lung. The analysis of tables 2 and 3 reveal that the motion of the collapsed lung parallels in its extent the motion of the overlying thoracic wall *in cases with the same degree of deflation*. Cases with the same degree of thoracic wall expansion show different ranges of pulmonary motions if the degree of deflation is different. On the other hand, different degrees of thoracic wall expansions may be accompanied by approximately the same respiratory motion of the collapsed lung, provided there is a corresponding difference in the degree of deflation. It can be seen, therefore, that, by means of radiological measurements, we are able to demonstrate and express numerically two important determinants of the respiratory motion of the pneumothorax lung: (*1*) the motion of the homolateral thorax, and (*2*) the degree of pulmonary deflation. Deviations from this relationship toward increased or limited motion of the lung were observed in several instances and can be explained by intrinsic and extrinsic factors that exert an influence upon the respiratory motion, such as limited extent of the diseased area, extensive fibrosis, consolidation, pleuropulmonary adhesions, bilateral artificial pneumothorax and the extent of the involvement in the contralateral lung.

A study of table 1 shows that the extent of the respiratory motions of the collapsed lung exceeded that of the homolateral thorax in all but two instances. In one of these two cases the initial treatment with the injection of 150 cc. of air was followed by a neutral final reading of the manometer. The other case had a very slight motion of the thorax,

TABLE 2

Relationship between the degree of deflation of the pneumothorax lung and the radiological respiratory ratios

SERIAL NUMBER	DEGREE OF DEFLATION	RADIOLOGICAL RESPIRATORY RATIO		REMARKS
		Pneumothorax lung	Overlying thorax	
26	30	58	92	
38R	35	60	91	Bilateral pneumothorax
34	36	65	92	
33	38	84	98	
30	39	62	86	
44	39	81	94	
41R	45	76	96	Bilateral pneumothorax
7	46	59	83	
13	49	60	79	
35	49	57	78	
17L	50	55	78	Bilateral pneumothorax
31	51	69	86	
20	53	54	80	
3	54	55	68	
21	55	57	75	
23	55	89	90	
25	55	59	77	
40	57	84	89	
1	59	56	76	
38L	59	66	88	Bilateral pneumothorax
24	60	72	85	
28L	60	60	73	Bilateral pneumothorax
10R	61	66	80	Bilateral pneumothorax
17R	61	81	90	Bilateral pneumothorax
19L	62	78	92	Bilateral pneumothorax
41L	63	67	78	Bilateral pneumothorax
48R	63	78	90	Bilateral pneumothorax
10L	65	73	76	Bilateral pneumothorax
18	65	69	82	
8	70	72	85	
11	70	84	93	
45	70	55	71	
48L	71	87	92	Bilateral pneumothorax
32	72	66	76	
39	72	71	80	
49	73	61	90	
12	74	78	86	
47	75	57	65	
51R	75	69	82	Bilateral pneumothorax. First treatment
27	76	81	88	
52	77	65	74	

TABLE 2—*Concluded*

SERIAL NUMBER	DEGREE OF DEFLATION	RADIOLOGICAL RESPIRATORY RATIO		REMARKS
		Pneumothorax lung	Overlying thorax	
2R	77	66	79	Bilateral pneumothorax. First treatment
51L	77	79	87	Bilateral pneumothorax. First treatment
9	77	72	84	
50	77	81	93	First treatment
36	78	61	67	
22R	79	72	82	Bilateral pneumothorax
2L	80	76	81	Bilateral pneumothorax. First treatment
16	80	67	74	
19R	80	79	81	Bilateral pneumothorax
28R	80	67	67	Bilateral pneumothorax
46	80	71	78	First treatment
37	82	73	78	
5	83	82	86	First treatment
15	83	99	99	
22L	83	68	74	Bilateral pneumothorax
43	84	79	87	
29	85	95	96	First treatment
42	87	75	87	
4	90	83	85	First treatment
6	95	99	97	First treatment
14	Measurement of thorax incomplete			

with a radiological ratio of 99. The difference between the radiological respiratory ratios of the pneumothorax lung and the overlying thorax was from 1 to 5 in 10 cases, from 6 to 10 in 15, from 11 to 15 in 17, from 16 to 20 in 7, from 21 to 25 in 5, from 26 to 30 in 3, and over 30 in 2 instances; in one case the thoracic measurements were incomplete. The respiratory ratios of the pneumothorax lung as a whole do not give a true idea of the extent of the respiratory motion of the diseased area of the lung. We have found that the motions of the diseased and uninvolved portions of the treated lung were approximately the same only in about one-fourth of the cases; in the remaining three-fourths of the cases widely divergent motions of the respective two portions of the lung were observed. It may be emphatically stated, therefore, *that conclusions based on studies of the motion of the entire pneumothorax lung are not applicable to the motion of the diseased portion of the lung.*

TABLE 3

Relationship between the expansibility of the homolateral thorax, the degree of deflation and the radiological respiratory ratio of the pneumothorax lung

SERIAL NUMBER	RADIOLOGICAL RESPIRATORY RATIO OVERLYING THORAX	DEGREE OF DEFLATION	RADIOLOGICAL RESPIRATORY RATIO PNEUMOTHORAX LUNG	REMARKS
47	65	75	57	
28R	67	80	60	Bilateral
36	67	78	61	
3	68	54	55	
45	71	70	55	
28L	73	60	60	Bilateral
52	74	77	65	
16	74	80	67	
22L	74	83	68	Bilateral
21	75	55	57	
1	76	59	56	
10L	76	65	73	Bilateral
32	76	72	66	
25	77	55	59	
35	78	49	57	
17L	78	50	55	Bilateral
41L	78	63	67	
46	78	80	71	
37	78	82	73	
13	79	49	60	
2R	79	77	66	Bilateral
20	80	53	54	
10R	80	61	66	Bilateral
2L	81	80	76	Bilateral
19R	81	80	79	Bilateral
18	82	65	69	
51R	82	75	69	Bilateral
22R	82	79	72	Bilateral
7	83	46	59	
9	84	77	72	
24	85	60	72	
8	85	70	72	
4	85	90	83	
30	86	39	62	
31	86	51	69	
12	86	74	78	
5	86	83	82	
51L	87	77	79	Bilateral
43	87	84	79	
42	87	87	75	
38L	88	59	66	Bilateral
27	88	76	81	

TABLE 3—*Concluded*

SERIAL NUMBER	RADIOLOGICAL RESPIRATORY RATIO OVERLYING THORAX	DEGREE OF DEFLATION	RADIOLOGICAL RESPIRATORY RATIO PNEUMOTHORAX LUNG	REMARKS
40	89	57	84	
23	90	55	89	
17R	90	61	81	Bilateral
48R	90	63	78	Bilateral
49	90	73	61	
38R	91	35	60	Bilateral
24	91	45	76	
26	92	30	58	
34	92	36	65	
19L	92	62	78	Bilateral
48L	92	71	87	
11	93	70	84	
50	93	77	81	
44	94	39	81	
41R	96	45	76	Bilateral
29	96	85	95	
6	97	95	99	
33	98	38	84	
15	99	83	99	
14	Incomplete measurements of thorax			

The respiratory motion of the diseased portion of the lung was studied in 36 cases, 31 with unilateral and 5 with bilateral artificial pneumothorax. Thus, altogether, 41 separate observations were made in this group. Cases in whom the disease involved more than two-thirds of the lung, or in whom no complete lateral separation was seen, were not considered for this study. The cases are arranged in table 4 according to their radiological respiratory ratios. It can be noted from this table that ratios varied from 50, indicating marked respiratory excursions, to 99, indicating almost complete absence of motion. The extent of motion can be visualized from the following grouping of the radiological respiratory ratios: there were between 50 and 59, 3 cases; between 60 and 69, 9; between 70 and 79, 9; between 80 and 89, 12; and between 90 and 99, 8. A comparison of the respiratory ratios of the diseased area, the uninvolved area and the overlying thorax is given in table 5.

An analysis of table 4 shows that the motion of the diseased area was less than that of the uninvolved area in 26, or 63.4 per cent. The motion of these areas was within ± 5 (arbitrarily taken as closely similar extent of motion) in 10, or 24.4 per cent. More motion was demonstrable over the diseased than over the uninvolved area in 5, or 12.2 per cent.

TABLE 4

The relationship between the radiological respiratory ratios of the diseased and uninvolved areas, the entire pneumothorax lung, and the overlying thorax

SERIAL NUMBER	RADIOLOGICAL RESPIRATORY RATIO				INTRAPLEURAL PRESSURE		AMOUNT OF AIR INJECTED	REMARKS
	Diseased area	Uninvolved area	Entire pneumothorax lung	Overlying thorax	Initial	Final		
							cc.	
17L	50	58	55	78	−7	−7	500	Bilateral
20	56	53	54	80	−9	−8	600	
13	57	52	60	79	−10	−5	400	
49	60	62	61	90	−12	−3	400	
47	61	56	57	65	−12	−8	300	
23	61	78	89	90	−6	−3	600	
42	63	78	75	87	−6	−2	500	
1	64	31	56	76	−10	−6	600	
17R	65	86	81	90	−11	−8	450	Bilateral
14	66	60	61	—	−5	−4	350	
18	66	70	69	82	−10	−8	600	
22L	69	68	68	74	−9	−9	400	Bilateral
37	72	74	73	78	−10	−6	500	
16	73	39	67	74	−10	−5	250	
33	73	89	84	98	−16	−8	500	
38R	73	57	60	91	−8	−4	300	Bilateral
39	74	71	71	80	−14	−6	500	
52	75	61	65	74	−8	−4	500	
19L	78	78	78	92	−11	−10	600	Bilateral
32	78	60	66	86	−9	−5	500	
25	79	51	59	77	−8	−4	500	
12	80	77	78	86	−8	−6	350	
46	81	40	71	78	−8	−5	300	
27	83	80	81	88	−10	−6	500	
38L	84	61	66	88	−8	−4	300	Bilateral
2R	85	62	66	79	−4	−3	500	Bilateral
30	85	42	62	86	−9	−4	500	
11	86	84	84	93	−7	−3	500	
48R*	86	74	78	90	−10	−4	400	Bilateral
35	87	49	57	78	−12	−6	500	
2L	88	71	76	81	−5	−3	300	Bilateral
19R	88	75	79	81	−10	−11	500	Bilateral
3	89	45	55	68	−13	−6	600	
4	91	79	83	85	−10	−8	500	
22R	92	58	72	82	−7	−5	500	Bilateral
31	92	64	69	86	−9	−5	500	
41R*	92	72	76	96	−10	−8	400	Bilateral
28R*	93	59	67	67	−11	−7	500	Bilateral
43	95	72	79	87	−10	−5	500	
29	97	72	95	96	−7	−6	350	
44	99	63	81	94	−16	−5	600	

* Extensive disease in the left lung

The respiratory expansion of the lung was measured before and during artificial pneumothorax in 11 cases. These data are presented in table 6. One can note from this table that the motion of the diseased portion of the treated lung was less than that of the entire lung before treatment

TABLE 5

Radiological respiratory ratios in 41 cases in which the diseased area of the pneumothorax lung was measured

RADIOLOGICAL RESPIRATORY RATIO	DISEASED AREA		UNINVOLVED AREA		OVERLYING THORAX*	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
Less than 40			2	4.9		
40–49			4	9.7		
50–59	3	7.3	8	19.5		
60–69	9	21.9	9	21.9	3	7.5
70–79	9	21.9	14	34.2	11	27.5
80–89	12	29.3	4	9.7	15	37.5
90–99	8	19.5			11	27.5

* The overlying thorax could not be measured in one case

TABLE 6

Motion of the lung before and during artificial pneumothorax

SERIAL NUMBER	RADIOLOGICAL RESPIRATORY RATIO			ENTIRE EXTENT OF PNEUMOTHORAX LUNG	REMARKS
	Lung before treatment	Diseased area of pneumothorax lung	Uninvolved area of pneumothorax lung		
4	65	91	79	83	
27	91	83	80	81	
28R*	64	93	59	67	Bilateral
29	86	97	72	95	
30	72	85	42	62	
31	73	92	64	69	
32	85	78	60	66	
37	73	72	74	73	
39	85	74	71	71	
46	72	81	40	71	
47	66	61	56	57	

* Extensive disease in left lung

in 6, or 54.5 per cent. The motion of these areas was closely similar (within ± 5) in 2, or 18.2 per cent. The extent of the motion of the diseased area after treatment was greater than that of the entire lung before treatment in 3, or 27.3 per cent.

We have calculated the radiological respiratory ratio in 47 healthy young adults, used as controls. A comparison of these ratios with that of the collapsed diseased area reveals that 19.5 per cent of the pneumothorax cases had a markedly high respiratory ratio, between 90 and 99, indicating very slight respiratory motions, that is not found in normal persons. Furthermore, the next lower bracket of respiratory ratios, between 80 and 89, includes 29.3 per cent of the pneumothorax cases and only 8.5 per cent of the controls. Respiratory ratios between 60 and 69 occurred more than twice as often in the controls than in the pneumothorax patients. It is rather surprising that in the group of the lowest respiratory ratios, between 50 and 59, there were 7.3 per cent of the pneumothorax cases and only 4.3 per cent of the controls.

TABLE 7

Comparison between healthy individuals and all pneumothorax cases

RADIOLOGICAL RESPIRATORY RATIO	DISEASED AREA OF PNEUMOTHORAX LUNG*		PNEUMOTHORAX LUNG ENTIRE EXTENT		CONTROLS	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
50–59	3	7.3	11	17.7	2	4.3
60–69	9	21.9	20	32.3	25	53.2
70–79	9	21.9	17	27.4	16	34.0
80–89	12	29.3	11	17.7	4	8.5
90–99	8	19.5	3	4.9		

* Cases with involvement of more than two-thirds of the treated lung were not included in this group.

These data suggest that a limitation in motion of the diseased pulmonary area can be attained by artificial pneumothorax in the majority of cases. There are, however, instances in which pneumothorax seems to increase rather than decrease the respiratory excursions of the diseased area.

CONCLUSIONS

1. The respiratory motion of the pneumothorax lung can be estimated with the aid of radiological measurements and can be expressed numerically in the form of the radiological respiratory ratio.

2. As long as the intrapleural pressure remains negative, the motion of the pneumothorax lung is determined mainly by the motion of the overlying thorax and by the stage of deflation of the treated lung.

3. The respiratory motion of the pneumothorax lung is proportionate

with the motion of the overlying thorax, provided the lungs compared are in approximately the same stage of deflation.

4. Deviations from this relationship may be caused by intrinsic or extrinsic factors, such as the extent and type of the tuberculous lesion, particularly the presence or absence of extensive fibrosis or consolidation, pleural effusion, wide-spread adhesions, contraction of the thorax, the condition of the respiratory muscles, and the extent and type of pulmonary disease in the contralateral lung.

5. The motion of the pneumothorax lung was greater than that of the overlying thorax in all but two instances.

6. The radiological respiratory ratio of the pneumothorax lung varied from 54 to 99, that is, from a marked range of motion to an almost complete absence of motion. The ratio was between 50 and 59 in 11 (17.7 per cent), between 60 and 69 in 20 (32.3 per cent), between 70 and 79 in 17 (27.4 per cent), between 80 and 89 in 11 (17.7 per cent), and between 90 and 99 in 3 (4.9 per cent).

7. A comparison with the controls reveals two important facts. First, respiratory ratios between 90 and 99, which were not observed in healthy individuals, occurred in 4.9 per cent only. Second, the percentage of respiratory ratios between 50 and 59, that indicate marked respiratory excursions, was four times greater in the pneumothorax group than in the control group.

8. Emphasis must be placed on the fact that *conclusions based on the studies of the motion of the entire pneumothorax lung are not applicable to the motion of the diseased portion of the treated lung.*

9. The respiratory motion of the diseased area of the pneumothorax lung was smaller than that of the uninvolved area in 63.4 per cent. The extent of the motion of these two areas was nearly equal in 24.4 per cent. The diseased area showed greater respiratory motions than the uninvolved area in 12.2 per cent.

10. If the radiological respiratory ratios derived from measurements on forced respiration are reduced proportionately to a level corresponding to quiet respiration, it is apparent that the motion of the diseased area of the lung can be substantially restricted by artificial pneumothorax.

11. Marked limitation in motion of the diseased area was induced by artificial pneumothorax in 19.5 per cent. This group had respiratory ratios between 90 and 99 that do not exist in normal individuals. Further comparison with healthy adults shows that the percentage of high respiratory ratios (between 80 and 89), that indicate limited motion, was

more than three times greater in the group representing measurements of the diseased area than in the controls.

12. There are certain instances in which pneumothorax seems to increase rather than decrease the respiratory excursions of the diseased lung.

13. A comparison between the respiratory expansions of the lung before and during artificial-pneumothorax treatment revealed that the motion of the diseased portion of the treated lung was less than that of the entire lung before treatment in 54.5 per cent; the motion of these areas was closely similar (within ± 5) in 18.2 per cent; the extent of the motion of the diseased area during treatment was greater than that of the entire lung before treatment in 27.3 per cent.

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SILICO-TUBERCULOSIS[1]

D. M. BRUMFIEL AND L. U. GARDNER

Silico-tuberculosis is the term used in America to describe a peculiarly chronic manifestation of tuberculosis that occurs only in silicotic lungs. The name implies that the process is primarily infectious but is modified by the reaction to silica. Its use is unfortunate because South African writers describe the same condition as tuberculo-silicotic. The reverse term, silico-tuberculosis, they reserve for cases in which the ordinary manifestations of tuberculosis are superimposed upon a background of generalized silicotic nodulation. "Concurrent silicosis and tuberculosis" is the synonym used by the Public Health Service in its Barre granite study. Since American usage has become more or less fixed it is difficult to change the terminology to conform with South African custom. We have therefore deemed it advisable to use the term silico-tuberculosis in the sense indicated.

Even thus limited, silico-tuberculosis is not yet thoroughly understood. This is shown by the fact that there are many dissenting opinions expressed by various observers. The cause of our misunderstandings and our delay in arriving at satisfactory conclusions lies in the fact that we have tried to rationalize from our knowledge of tuberculosis and of silicosis and have built up the conception that silico-tuberculosis must represent a simple summation of the two.

Had we approached this problem with no preconceptions as to what it should be, but with completely open minds as if it were a new clinical entity, we would be much further ahead in our understanding than we are now. Too often the cases under observation failed to satisfy some of the criteria of diagnosis or of clinical behavior which we had led ourselves to expect in our hypothetical reasoning. Something was evidently wrong and too often we assumed that the wrong lay in the claims of our fellow observers and charged them accordingly.

We can quickly come to a common ground of understanding and progress in medical thought on this subject if we accept as the starting point

[1] From the Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation, Saranac Lake, New York.

the basic principle that "silico-tuberculosis is neither silicosis nor tuberculosis, nor is it a simple total summation of the two, but it is a distinct disease entity with certain characteristics peculiarly its own."

The earlier observations were made upon clinical material, which by its very nature presented two widely separate phases of development. First, and most numerous, were those cases in which tuberculosis had already gained ascendency, had become progressive and was usually far advanced. These were seen in the tuberculosis clinics, hospitals and sanatoria; they were totally disabled and differing in no essential from other progressing fatal cases of tuberculosis.

On the other extreme were a few scattered instances usually picked up incidentally in the course of the investigation of some other clinical condition or in the attempt to make a differential diagnosis of some atypical pulmonary complaint. Here the evidence was either exclusively or preponderantly roentgenological. Therefore, many of us, steeped in the tradition that a positive sputum is the *sine qua non* for diagnosis of any form or degree of pulmonary tuberculosis, denied the possibility of the X-ray shadows being caused by tuberculous lesions because we failed to demonstrate bacilli.

Thus we had the beginning and the end of the story and the two extremes were difficult to reconcile and coördinate. The intervening chapters, containing the evolutionary phases of the history, were lacking. They are now being supplied by the serial examination of thousands of men in the dusty trades, which is being conducted by various agencies throughout the country. The contribution thus made to medical knowledge will prove to be incalculable.

Silico-tuberculosis presents certain consistent features which serve to set it apart from common uncomplicated tuberculosis and from the non-tuberculous pulmonary diseases as well. (*1*) It appears in the later decades of life, usually the fifth and sixth. (*2*) It has a strong tendency toward chronicity and a low grade of toxicity. (*3*) Tubercle bacilli are difficult or impossible to demonstrate until late in the course of the disease.

First, as to its late appearance in the life span, it is true that ordinary tuberculosis makes its clinical début in the 40 to 60 age groups in an occasional individual, but the vast majority occur before thirty. In contrast, cases of silico-tuberculosis do not generally evolve into the clinical stage before the age of forty and many may be delayed until fifty or later.

As to the chronicity and low toxicity, it seems almost as though a symbiotic relationship had been set up between the tubercle bacillus and the human host, so occult may the pulmonary lesions remain for long intervals of time, even years in some instances. Routine roentgenograms reveal the shadow patterns characteristic of these lesions in individuals who are apparently in perfect health except that they usually exhibit more or less dyspnoea. This appearance of health is substantiated by a total lack of toxic symptoms, even upon searching inquiry. In serial films, these shadows may appear stationary, or they progress very slowly over long periods of time even though the individual has remained at hard physical labor in the interim. Occasionally, extension of the lesion is evident, even to the point of cavity formation, and still without evidence of toxicity in the form of those constitutional symptoms which are so commonly associated with ordinary tuberculosis. Doubtless in some few of these the "symbiosis" is so complete that the embers are never fanned into flame and the pulmonary disease remains occult until death ensues from some other cause. However, in many individuals the time finally comes when the delicate balance of power between host and organism is broken down and tuberculosis sweeps on its course. Here again the usual toxic manifestations are frequently so delayed or so mild that the disease has become well advanced before its true nature of active, progressive tuberculosis has been suspected.

Again, the difficulty of demonstrating bacilli in the sputum prior to the florid extension of tuberculosis interferes with diagnosis in those stages which carry favorable prognosis. This fact, of itself, has complicated the problem and delayed treatment in many cases. Some observers have not been willing to admit the possibility of a tuberculous lesion in the face of negative sputa. Yet microscopical examination of the lung tissue after necropsy has revealed the characteristic pathological anatomy of modified tuberculosis. When once the tuberculous element gains the upper hand and becomes progressive and clinically active, typical acid-fast bacilli are demonstrable by routine methods.

The histological picture offers an explanation for this apparent paradox. Advanced silico-tuberculosis is neither that of silicosis superimposed upon a preëxisting focus of tuberculosis nor the reverse. It appears more like a mixture of reactions to both tubercle bacilli and to silica in the same area. The rudiments of organizing tuberculous granulation tissue and a modified silicotic fibrosis, often not nodular in form, can be identified.

Nevertheless foci of silico-tuberculosis frequently begin about imperfectly healed tuberculous lesions. The inhaled silica particles tend to accumulate in excessive numbers at the edges of the tuberculous scar. They alter the character of that scar and cause its fibres to become very thick and heavy; they form some nodules in and about it. As more dust accumulates the area of reaction increases in size. In time, wandering phagocytes transport particles of silica into the interior of the focus. If living tubercle bacilli are still there, the silica causes them to multiply. In case the fibrous investment is not too thick, the phagocytes, in time, carry some of the microörganisms out to its surface and the infection spreads to other parts of the lung. This series of events has been observed repeatedly in experimental animals.

If, on the other hand, bacterial proliferation does not start until a very thick zone of fibrosis has developed, the stimulating influence of silica is almost balanced by other factors which are unfavorable to the growth of the tubercle bacillus. The blood and lymph supply in such an area of dense fibrosis is generally limited. Nutrition is barely adequate to keep fibrous tissue alive; sometimes, in fact, it is reduced to the point where anaemic necrosis develops. The oxygen tension must in consequence be lowered. The aerobic tubercle bacillus does not thrive in such an environment. Microörganisms are so infrequent that they are rarely found in stained sections although their presence can be established by animal inoculation. But apparently the silica keeps enough of them alive so that small amounts of tuberculous granulation tissue continue to form. This is constantly being acted upon by the silica and transformed into dense, obliterating fibrosis. The two irritants together ensure a sluggish progression of the lesion. After many years the bacilli may reach the periphery and more rapid extensions into uninvolved parts of the lung then occur. Not infrequently cavities now develop which destroy the scar tissue but these are almost invariably late manifestations.

The pathological reaction explains the clinical course of silico-tuberculosis. The sputum remains negative because the bacilli are tightly locked up in dense scar tissue. Symptoms of intoxication are lacking because the tissues are not degenerating to any extent and the blood and lymph supplies to the area are so reduced that absorption is limited. When infection finally spreads beyond the limits of the fibrosis more normal lung is invaded and then the classical symptoms of tuberculosis are manifested.

Silico-tuberculosis causes little intoxication but it practically always produces dyspnoea of varying severity. It replaces and destroys a considerable portion of the capillary bed of the lungs; it is associated with chronic adhesive pleurisy, which tends to immobilize the lungs, and with compensatory emphysema, which has its usual effect upon pulmonary function.

The circumstances under which silico-tuberculosis develops operate against the welfare of its victim. He is a hardy, usually robust, individual engaged in strenuous physical work. By nature, and by code, he is a "hard guy" given to contemptuously waving aside all recognition of minor ailments, and by the same token considers all ailments as minor unless they actually disable him. He wants to keep his place on the payroll and to deliver his daily share of physical accomplishment. These personal characteristics, added to the occult nature of the disease and its insidious evolution, lead him into the position of following the very worst possible course for any human being with tuberculosis, namely, doing hard physical work in the face of active and progressive disease. The part played by the coëxisting silicosis in the later clinical progress is still undetermined.

In contrast to these cases of silico-tuberculosis there is the picture of the individuals in whom ordinary tuberculosis develops on a background of silicosis[2] without the "symbiotic" or "pseudo-symbiotic" silico-tuberculosis stage and steps of evolution. Such cases fall rather sharply into two clinical groups, the first, which behave as do other cases of ordinary uncomplicated tuberculosis, with the possible exception that in some instances the coincidental silicosis seems to accelerate the progress of the phthisis. The second group consists of those spectacular, but rare, examples of acute tuberculosis with coëxisting silicosis. The latter are usually first manifested by a zone of inflammatory reaction about each silicotic nodule and then progress like exogenous primary infections, with rapid extension and uncontrollable progression.

While the whole group of "superimposed" tuberculosis is not large numerically, it has been the cause of much of our confusion. Since this form of the infection manifests itself by symptoms that are in no way different from those of tuberculosis in the rest of the population, observers have felt that the clinical picture of silico-tuberculosis should likewise be so manifested. When we learn to consider the two groups separately, as a

[2] In South African terminology these are the only ones which should be designated as silico-tuberculous.

study of their pathology seems to warrant, and when the evolution of a sufficient number of each type of case has been followed in serial roentgenograms, our ideas about both conditions will be clarified.

The following plan is urged as providing at least a partial solution to the problem of preventing unnecessary illness, disability and even death. All individuals shown to have characteristic, or even suspicious, shadows in routine roentgenograms should be subjected to close supervision. They should be reëxamined frequently, at perhaps quarterly intervals, in spite of their loud protestations of perfect health. If their pulmonary lesions show no progressing changes, they may be allowed to work but preferably at a job that involves less physical exertion. But, if, and when, roentgenographic evidence of such progression does appear, the ideal procedure would be to remove individuals so affected from active duty, irrespective of their apparent clinical condition, and put them on the routine rest treatment for active tuberculosis under medical care. Practically, however, this is likely to be difficult to carry out with the rank and file of workmen, chiefly for psychological reasons. Not being in the higher brackets of intellectual attainment, unaccustomed to any form of abstract thinking, particularly with reference to grasping long-range health problems, they cannot reconcile their lack of actual disability with any necessity for treatment. Therefore at this stage many would undo the advantages of physical rest by mental unrest, bewilderment, rebellion and fancied grievances at being discriminated against. Just such conditions were encountered in the South African experiences, and it may well be necessary in dealing with such individuals to compromise, at least temporarily, by transferring such workers to some other employment, which involves a minimum of physical exertion. Close medical supervision would be carried out in the meanwhile. With men of superior intelligence, such as those who have risen to responsible positions, the more ideal program of immediate rest can be put into effect promptly. Such men, who could grasp the full implications of the situation at once, have done very well indeed on such regimen.

In this way, many lives will be saved, many individuals who would otherwise become permanently disabled may be restored to employment, and sources of tuberculous infection will be eliminated from the plant and the community. The general adoption of such a far-sighted procedure in industry would ultimately benefit employee, employer and society at large.

THE EFFECT OF RADIO SHORT-WAVES ON TUBERCLE BACILLI AND TUBERCULOSIS[1]

H. J. CORPER, MAURICE L. COHN, M. G. SIMPSON AND C. BOWER

As one scans the field of the physiology and therapeutics of the various currents and radiations (1), he is impressed with the unlimited possibilities still undisclosed in these fields and the restricted information available from conventional experiments with the present equipments and currents. Yet, when in the course of tests, apparently reliable investigators record positive observations, further corroborative and explanatory evidence is desirable. In certain diseases, the effect of physical agents has yielded striking and readily explained results. The destruction of strains of the gonococcus in the tissues by means of heat is a classical illustration, but in other diseases the use of heat alone has proved of little avail. This was found to be the case with the tubercle bacillus, which could grow readily at a temperature (42°C.) well in excess of that tolerated by the tissues of the body for any length of time (2). However, in the use of the radio short-wave therapy in tuberculosis, the problem is complicated by the possibility that other factors may be at play capable of destroying the bacilli and that heat plays no significant part in their destruction.

The clinic gives little more than purely subjective information of a type which will be presented later in an illustrative case. The experimental data, though of greater value, are not sufficiently exhaustive and are complicated by technical difficulties which raise the question whether the observations are the result of undetermined additional factors such as point heating, etc.

In a recent communication on the physiological basis of short-wave therapy, Wolf (3) concludes that short-waves have a marked influence on acute and subacute inflammatory processes, on rheumatoid arthritis and local oedema, but that they have no effect on regenerative processes and thus have no influence on the healing of wounds and the formation of callus. The action appears to be due to heating, no proof having been found for a specific action on different tissues by the various wave

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

lengths. Within the past year, Liebesny (4) points out that short-wave therapy as used by him is an athermic short-wave in contrast to the more or less intense heating of diathermy. Athermic short-wave therapy exerts a biological action which, in some cases, is the opposite of heat actions. By excluding heat action as much as possible, favorable therapeutic results were obtained in suppurating and inflammatory processes, on the surface of the body as well as in the deeper parts.

The enthusiasm with which short-wave therapy has been accepted is evident from the appearance of two editions within two years of Schliephake's recent book (5). In the last, 1936, edition, he points out that in contrast to diathermy, in which the maximum heating is on the surface of the tissues, the short-wave procedure exerts its maximum action in the inside of the body. Localized inflammatory foci are heated better than normal healthy surroundings because the dissipating blood circulation is lacking. Aside from the heat effect, the short-wave therapy also has a specific action on the tissues. In human pulmonary tuberculosis, he admits that the available data are still too limited, and he suggests further observations. He is enthusiastic regarding the value of short-wave therapy.

On the other hand, Kowarschik (6) expresses a certain skepticism in regard to the healing effect of short-waves, especially in acute inflammatory diseases. He views it as a modification of the older procedures for applying heat, only in rare cases exceeding these methods in effect.

The following case is illustrative of what may be met clinically in the use of short-wave therapy and must eventually be interpreted in the light of experimental studies, elaborated by *in vitro* cultural and static tests.

Briefly, the patient was 36 years of age with no family history of tuberculosis. While in Army service in the Philippines as a radio operator in 1922, he suffered repeated colds and pneumonia during the rainy season. After discovery of pulmonary tuberculosis in 1924, only home treatment was observed until 4 years later when weakness, night sweats, cough and pyrexia made sanatorium residence essential at a Veterans' Hospital. He remained there for about 18 months and then returned to his home in a small town in Dakota. In 1931 he moved to Denver for his health but was unable to work. From 1930 to 1933 he had very little medical care and was rated totally disabled. In 1933 he was examined by the tuberculosis division of the Denver General Hospital, and sanatorium treatment was advised. From 1933 on, the patient remained ambulant, carried on university courses and irregular radio work. In 1934, he became acquainted with the use of short-wave radio treatment and began

to treat himself, starting with large coils and long wave-lengths, and trying various methods of general and local chest treatment. From 100 metres originally used, the wave-length was reduced to 16 metres and the time varied to an average of about 3 minutes, 30 minutes being too long because of undesirable results upon the general condition of the patient. The patient noted a definite stimulating effect from the treatment and an apparent relief from chest pains. His own conception was that the short-wave treatment, carried out regularly from 1934 to 1937, resulted in a gradual but definite improvement in his general well-being. He also noted that appropriate short-wave treatment resulted in a decreased sputum, while larger exposures tended

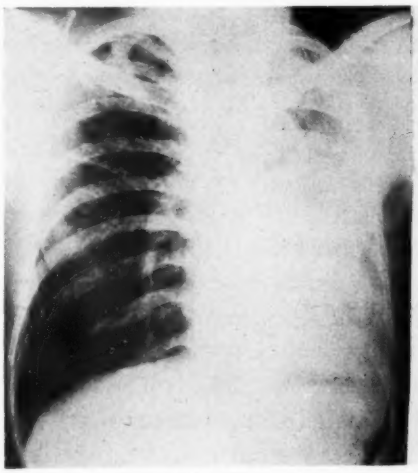

FIG. 1

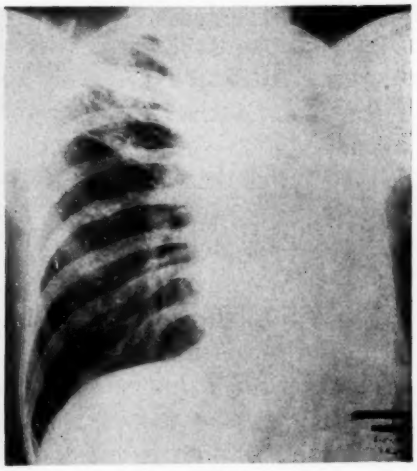

FIG. 2

FIG. 1. Roentgenograph taken of patient in 1933 before radio-wave therapy
FIG. 2. Roentgenograph taken in 1936 after 2 years of radio-wave therapy

to increase it. Tubercle bacilli had been found consistently in the sputum since 1928 and are present in large numbers at this time. The roentgenological report of the chest in 1933 (figure 1) was: "The left lung is obscured throughout by thickened pleura, infiltration, upper lobe cavitation and displacement of the mediastinum to the left (signs of long standing chronic pulmonary tuberculosis). The right upper and middle lobes show peribronchial and parenchymal infiltration, fibrosis, thickening of lobar pleura, and moderate cavity formation, presumably fibrosed (signs of more recent but healed or healing chronic pulmonary tuberculosis)." The roentgenological report in 1936 (figure 2) was: "entire left chest homogeneously dense with exception of upper half which shows areas of increased translucency. Right middle and upper third studded with numerous small type calcifications. Apex shows marked

infiltration, fibrotic changes combined with some honeycombing in clavicular region. Heart and trachea markedly displaced to the left. Right diaphragm and costophrenic angle normal. Conclusions: fibrous (interstitial) pneumonia, left, combined with cavitation in upper half. Tuberculosis of predominantly fibrous character in right upper lobe, exudative cavitation in right apex." Although it must be admitted that there has been some progression of the tuberculosis in the chest between 1933 and 1936, as is to be noted by comparing the X-ray films, yet apparent symptomatic relief is claimed by the patient from the short-wave therapy.

This can be considered, as so often happens in trials on human beings, as "only another case;" and multiplication by hundreds of similar cases would give no more accurate information. Unfortunately, the literature on animal tests, so desirable in settling such questions, may also yield inconclusive information.

Among the first experimental reports on tuberculosis and short-wave treatment was that of Haase and Schliephake (7) in 1931, who in an extensive article point out that the first experiments on destroying bacteria by means of electrical waves were performed by Schliephake in 1927 but were inconclusive up to 1929. They finally used 4.8 metre waves and controlled the experiments by using heat alone. Human tubercle bacilli in physiological salt solution were killed in 10 minutes with the short-wave in contrast to 30 minutes with heat alone. The survival curve showing the effect of heat and short-waves on human tubercle bacilli in salt solution is presented and includes the results of temperatures from 55°C. to 80°C. and the time up to 30 minutes. The results obtained at 53°C. showed a relative difference between heat alone and heat produced by short-waves, but only exact determinations at this temperature could be admissible. They also studied ranges from 3 to 100 metres and noted peaks in which the bacilli were more or less affected; wave lengths of 35 and 98 metres appeared innocuous, but those of 31.5, 95 and 103 metres showed marked retardation. As a whole, the harm to the bacilli was less marked with long than with the short waves (3 to 20 metres). Guinea pigs and rabbits infected in the joints of the legs showed a definite retardation of the infection by short-wave treatment although marked variations occurred. The effect on the general disease in the guinea pig was lacking. In rabbits with two joints infected and one treated, a striking contrast was noted. In final analysis, Schliephake admits the entire action was possibly that of heat, although one cannot exclude a pure wave effect. All his experiments were of the short interval type.

In various experiments on guinea pigs, reported by Beerens and Remouchamps (8) in 1935, they gave daily exposures for 10 minutes with short-waves (5 metres), following subcutaneous infection with a bovine strain of tubercle bacilli (Vallée) and BCG. No influence of the short-wave exposures was noted on the course of tuberculosis in any of the experiments.

Likewise, Vercesi (9) used short-waves for treating ten rabbits, infected intravenously with 0.1 mgm. of bovine tubercle bacilli (strain Vallée), the exposure being for 5-minute intervals in five rabbits, and 10-minute intervals in the other five, with ten rabbits for controls. The apparatus "ultratherm" was used with wave length of 5.75 metres. No healing effect was noted. Section of the rayed rabbits' lungs revealed a pulmonary hyperaemia which was more marked in the animals exceeding 5-minute interval exposures. They believe the hyperaemia of the lungs, referable to the heating effect of the short-waves, contraindicates the use of larger doses in pulmonary tuberculosis. Their findings do not agree with those of Haase and Schliephake. Liebesny (10) felt encouraged with his results and justifies the further use of short-wave therapy in tuberculous diseases.

Within the past year, 1936, in this country, Kling and Rubin (11) reported on studies in guinea pigs, which appeared to bear out the opinion of Schedtler (12) that the eventual beneficial effect on human tuberculosis is apparently due to hyperaemia and heating rather than to any specific action. In a group of ten guinea pigs treated with three different modalities in the electric and electromagnetic fields of a 6 metre ultrashort-wave apparatus no influence was noted on the development and progression of the tuberculous lesions as compared with a large control group. Weak or strong dosage, as evidenced by a slight or marked rise in temperature, did not seem to have any influence on the development of the tuberculous process. With 20 to 21 exposures during the course of 3 months, 10 animals showed no deleterious effects or complications.

One of the greatest obstacles to an interpretation of apparently simple experiments on bacteria or lower forms of life is the heat factor involved. As a result of their study of bacteria of various types, Fabian and Graham (13) state, "It is apparent from these data that a frequency of 10 megacycles per second (about 30 meters) is by far the most effective frequency studied. This was true both for the animals studied and for bacteria . . . the reason for the greater effectiveness of the displacement current at this frequency was due to its ability to increase the tempera-

ture." They also say, but do not prove, "It is believed that, although temperature doubtless plays an important part in causing the death of bacterial cells and under the conditions outlined in these experiments, it is not the only factor involved."

In 1935, Gale and Miller (14) found no bactericidal effect of short- and ultrashort-waves on staphylococci, streptococci, pneumococci or typhoid bacilli when the temperature was controlled.

EXPERIMENTS

Our experiments with ultrashort-wave therapy were initiated about three years ago under the stimulus of the reports in the literature and the apparent symptomatic clinical results. In the earlier work, we were content to use a commercial spark-gap machine and a variable wave-length. These experiments proved unsatisfactory and unconvincing, and it was decided to set up an apparatus suited to definite wave-lengths and purposes of experiment. In this we were materially assisted by the Department of Physics of the University of Denver. Realizing, however, the extreme range of possibilities, we finally determined to work with only a few definite wave-lengths and under carefully controlled conditions. For this purpose we chose a linear oscillator, using two to four no. 210 radiotrons in parallel push-pull and supplying the plate with 600 volts with unrectified alternating current of 60 milliamperes. This outfit was used to deliver 2.8 metre waves.

For exposing suspensions of tubercle bacilli, the condenser field consisted of a large carton with metal bottom and inner surface covered with tinfoil. In the centre of the carton was placed a smaller tube covered with tinfoil and insulated from the bottom so that the radio frequency field was homogeneous between the inner and outer electrodes, the interspace being used for the exposure tubes (figure 3). These exposure tubes consisted of small bacteriological glass test tubes, plugged with paraffin cotton and cork stoppered to prevent drying. Each tube contained about 4 cc. of suspension. The individual tubes were used to avoid contamination, one being removed for each sampling and replaced by a similar tube.

In the animal experiments, the entire guinea pig was maintained with food and water, for long interval experiments, between tinfoil electrodes which completely covered the top and bottom of the small confinement. In this way the animal remained in the field regardless of his movements; and the field was tuned by means of a radio frequency metre for maximum

current density. Preliminary tests were made to adjust the exposure for the animals to a maximum density and yet avoid an excessive elevation of body temperature, especially when the effect of the waves themselves without heat production was desired. An elevation of about one degree (rectally) was not considered significant for guinea pigs.

Experiments on bacillary suspensions and on infected guinea pigs were carried to a limit of practically continuous exposure up to about 30 days.

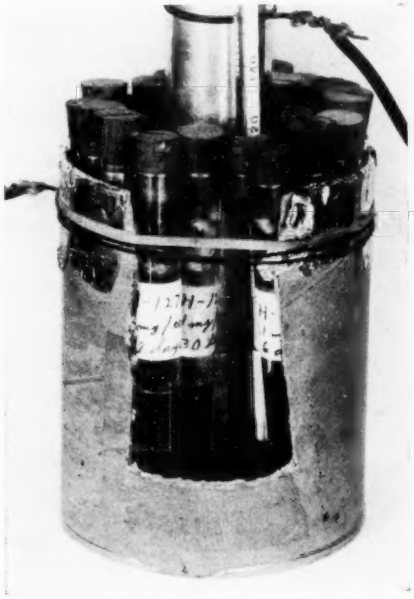

FIG. 3. Exposure equipment used for determining the effect of radio short-waves on suspensions of tubercle bacilli. The front of the container and tinfoil have been cut away to show the tubes, thermometer and centre condenser field. At room temperature or 37°C. human tubercle bacilli remained unaffected after 30 days' continuous exposure to 2.8 metre waves.

The purpose of this was to exhaust as far as possible the limitations of pure wave (free from heat) action. The shorter intervals were initiated as single short-wave exposures of about 5 to 30 minutes up to 2-hour intermittent daily exposures.

The Effect of Radio Short-Waves on Tubercle Bacilli: In earlier preliminary experiments where exposures of 5 to 30 minutes were used, the wave-lengths ranged from 4.8 metres to 186 metres with no apparent

bactericidal effect upon fine suspensions of varying concentrations, ranging from 0.01 mgm. to 0.000,001 mgm. of tubercle bacilli per cc. suspended in 0.9 per cent sodium chloride solution. From this work we concluded that the intervals of exposure should be extended, at the same time avoiding heat effects as far as possible and, in addition, to try shorter waves on the basis of the theory of possible specific action of greater frequency currents.

Two sets of experiments will be reported here, one at room temperature using a wave-length of 2.8 metres with a current density of 500 milliamperes and extending over 30 days of continuous exposure on suspensions of virulent and avirulent human tubercle bacilli (0.1 mgm. per cc.) in fine suspension in a buffered solution (2) at pH 7.0; the second experiment is identical in detail to the former, except that the power was increased to maintain the tubes containing the suspension of tubercle bacilli continuously at about 37°C. and running the control tubes at incubator temperature. In all these *in vitro* experiments, samples were taken to determine the viability of the bacilli by planting on a good nutrient medium (15) at intervals of 2 to 3 days.

The amount and type of growth was identical in both of these experiments from samples taken from exposed and control tubes. The exposure to the radio waves of 2.8 metres at room temperature or at incubator temperature (37°C.) exerted no appreciable effect upon the viability of four different strains of human tubercle bacilli in fine suspension in a buffered solution at pH 7.0 up to 30 days.

The Effect of Radio Short-Waves on Experimental Tuberculosis: In a previous report (2), concerned with the effect of heat on tubercle bacilli *in vivo*, among other means of producing heat was included radio short-waves, and exposures were carried to the point of producing acute burns in rabbits' ears without appreciably affecting the viability of the tubercle bacilli injected intracutaneously in graded amounts. An illustrative experiment on this was recorded in table 4 in this paper in which 60 metre radio-waves (5,000 kilocycles) were used at 2-hour intervals daily for a total of 24 hours with no effect. Other wave-lengths within the range of our experimentation proved equally inactive.

To test the effect of prolonged radio short-wave treatment on the development of experimental generalized tuberculosis in the guinea pig, a series of guinea pigs was infected intravenously with 2 cc. of a 0.01 mgm. per cc. of fine suspension of a recently isolated virulent human strain of

tubercle bacilli (H127). These animals were divided into two groups, one group was subjected continuously to 2.8 metre short-wave treatment for 30 days, while the second group served as control. In addition, non-infected guinea pigs were treated to observe any effect of the ray treatment itself. All the infected animals, treated or not, showed a loss of weight, which was not evident in the noninfected guinea pigs whether rayed or not. At the end of the experiment, lasting 30 days, autopsy showed no difference between the treated infected pigs and those only infected but not treated. Raying alone caused no appreciable gross changes in the uninfected guinea pigs. The infected guinea pigs all showed a generalized moderate amount of tuberculosis.

It is evident from all the foregoing experiments that radio short-waves were not found to exert an appreciable detrimental effect on virulent human tubercle bacilli even when exposure was continued as long as 30 days without intermission and the bacilli remained at room or incubator temperature. Likewise, no effect was noted of radio short-waves upon experimental tuberculosis in the guinea pig, intravenously infected and treated to avoid excessive elevation of body temperature during this time. Radio short-waves applied for short intervals to the point of causing definite tissue injury failed to exert any effect upon the viability of tubercle bacilli.

These observations lend support to the view expressed recently by Mortimer and Osborne (16) who maintain that there is no conclusive evidence . . . of a specific biological action of high frequency currents; and since it was previously shown that heat *per se* is not able to destroy tubercle bacilli *in vivo*, short-wave radio therapy cannot be considered as yet a justified therapy in tuberculosis.

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THE EFFECT OF CONTAGIOUS DISEASES ON PULMONARY TUBERCULOSIS AND ON THE TUBERCULIN REACTION IN CHILDREN[1]

J. P. NALBANT

It has been taught that certain contagious diseases, such as measles, whooping-cough and influenza, exert their most serious effect upon children through the influence they have upon the tuberculous infection or the tuberculosis that they may have. These diseases are reported by many to predispose to tuberculosis and to aggravate and make worse existing clinical tuberculosis. Also, they have been thought to depress or obliterate the child's capacity to react to tuberculin. This opinion is expressed in numerous recent works on both tuberculosis and contagious diseases of childhood.

In his textbook on *Pulmonary Tuberculosis*, Fishberg wrote that "a state of anergy is produced during an attack of measles, therefore the tuberculin test becomes negative." Krause in his article on *Environmental Factors in Tuberculosis* stated that "measles may profoundly depress the allergy of the body." Willis in his book on *Laboratory Diagnosis and Experimental Methods in Tuberculosis* put forth the same idea. Veeder asserted that "the effect of intercurrent infections, particularly measles, is well known and the development of activity in many cases of tuberculosis can be traced directly to them." Debré and Papp studied 37 tuberculous children who developed measles. The tuberculin test, done by the Pirquet method, showed that the reaction became negative in all at the appearance of the eruption, but became positive again in half of them by the seventh day. Mitchell *et al.* asserted that positive reaction to tuberculin is approximately 264 times as frequent during the convalescent, afebrile stage of measles as during the febrile stage. Wachter found a marked delay in sedimentation in tuberculous children for several weeks after measles, which fact, he thought, proved the inhibiting influence of the infection on immunity. He thought that the sedimentation test might give early warning of a menacing or beginning tuberculosis after measles.

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

A view opposite to those described above has been taken by Myers, Chadwick and others. Chadwick studied a group of tuberculous children who had reacted positively to tuberculin and who showed no change roentgenologically in their disease, and no change in their reaction to tuberculin during and after measles. Berghoff studied 596 cases of measles in the Army. He could find only one case of frank active tuberculosis following directly after a measles infection. Beisken took a skeptical attitude concerning reactivation of tuberculosis by measles.

As to the effect of whooping-cough, chickenpox, scarlet fever and mumps on the tuberculin reaction and on active or inactive tuberculous lesions, little work has been done in this country. In Germany, Beisken studied 200 cases of whooping-cough and concluded that it had very little to do with the development of tuberculous meningitis in infants. In France, Debré found that only 8 per cent of his cases had had whooping-cough, and this had preceded the onset of tuberculosis by more than six months. Engel admitted that the rôle of whooping-cough in tuberculous meningitis or miliary tuberculosis is very doubtful. Bernard and Lamy studied 18 cases, between the ages of 3 months and 2 years, and concluded that the theory that whooping-cough initiates or causes extension of tuberculosis is greatly exaggerated. Our own experience supports the contention of this latter group of workers.

At the Wm. H. Maybury Sanatorium we have studied 43 children with measles, 39 with chickenpox, 16 with whooping-cough, 13 with scarlet fever, 30 with mumps and 6 with diphtheria, making a total of 147 cases of acute infectious disease in a group of children convalescing from pulmonary tuberculosis of the childhood type. Several of the children contracted two or more of these diseases at different times during their stay at the Sanatorium. The total number of children was 118. Their ages ranged from 6 months to 15 years. No special note was made as to race or sex. All had X-ray examination of the chest a short time before the onset of the contagious disease and directly after the expiration of the quarantine period. Thus any roentgenological evidence of progression or reactivation of the tuberculous disease was noted. Eighty-three of the 118 children had active pulmonary tuberculosis of the childhood type. The remaining 35 had quiescent or apparently arrested disease.

Twenty-seven of the 43 cases of measles were tested intracutaneously with Old Tuberculin before, during and after the acute infectious disease.

All were positive before measles developed. Four became negative to a dose to which they were positive before, but were again positive two weeks after the disappearance of the eruption. Two of the four who became negative during the eruption had given only a faint reaction to their first dose of tuberculin before measles, and their reactions after measles were again only faintly positive. In this group of 43 there were 32 cases of active childhood-type tuberculosis with parenchymatous lesions and 11 cases of quiescent or apparently arrested disease. It was found that 6, or 14 per cent, had shown an increase in the preëxisting tuberculous process as shown by roentgenological examination. None of the 6 exacerbations, however, occurred in less than one month after the measles. Two of them were detected two months after the measles had subsided, one, one month after, one, four months after, and two, five months after. They all recovered completely in a few months. In each instance the exacerbation of the tuberculosis was an evanescent occurrence. The extension of the tuberculous lesion occurred only in the group that had active disease at the time of the onset of the measles.

There were 16 children who contracted whooping-cough in the Sanatorium. Of these, 13 had active pulmonary lesions and 3 were considered quiescent or apparently arrested. Of this group 2, or 12 per cent, showed exacerbation of the tuberculous disease. Of the 2, one occurred during the course of whooping-cough but promptly subsided. Unfortunately, none of these was tested with tuberculin during the intercurrent infection.

The group of children with chickenpox consisted of 39 children, of whom 21 had active and 17 had quiescent or apparently arrested childhood-type tuberculosis. Three, or 7.5 per cent of them, experienced extension of their lesions. In none of this group was there any apparent change in the tuberculin reaction either during or after the chickenpox.

The effect of mumps on the tuberculin reaction was unexpected and surprising. Of the 25 children with mumps who received tuberculin before and after the disease, 24 were positive at both times, one being negative to both tests. However, a change in the type of reaction was noticed in a large number of them. Eighteen of the 24 showed from moderate to marked increase in size and duration of the reaction to tuberculin. Two showed decreased reaction. In spite of this manifest increase in sensitivity, none of the patients showed reactivation or exacerbation of their tuberculosis.

Of the 13 cases with scarlet fever only one showed a spread of the

tuberculous process. None of the 6 cases of diphtheria experienced any ill effects so far as their tuberculosis was concerned. The children with scarlet fever and diphtheria were not tested with tuberculin.

DISCUSSION

In this group of 118 children with 147 cases of acute contagious disease, we have found only 12 in which the tuberculous disease showed any demonstrable increase in the roentgenogram at various times during convalescence. This fact is not at all surprising, because a study of the course of tuberculosis in children without these complications (Nalbant) indicated that exacerbations or remissions of childhood-type tuberculosis are fairly common occurrences. The percentage in this study was approximately 12 per cent, which figure closely parallels the percentage of extension of tuberculosis seen in the group of patients with acute contagious disease.

On the basis of these data and those reported in the literature, it is evident that the much dreaded diseases such as measles and whooping-cough seem to have very little, if any, effect on a tuberculous lung. Again in the great majority of those who showed increase in tuberculosis, the extension occurred several weeks after the intercurrent disease had subsided. It seems quite evident that the increase in the tuberculous process seen in this group of children was due to an endogenous reinfection from a preëxisting diseased area, rather than being influenced by the contagious disease. It was also noted that none of these remissions occurred in quiescent or apparently arrested lesions, showing that the old foci were not disturbed by the intercurrent, contagious disease. The remissions seen in the active tuberculous lesions could be safely considered coincidental and unrelated to the contagious disease.

The effect of diseases such as measles and whooping-cough upon the tuberculin reaction may well be reconsidered in the light of such data as these. During the course of study very little evidence was found to support the contention that measles or any of the other contagious infections have a depressing effect on the body's capacity to react to tuberculin. It is an established fact that the Pirquet test is less sensitive than the Mantoux test, which is often positive where the former was negative. The majority of workers who have reported that measles and certain other diseases have a depressing effect on the tuberculin reaction used the Pirquet method. This may explain the apparent discrepancy, because the Mantoux test was used in all of our cases. We are

of the same opinion as Hart, who believed that the majority of reports have been based on experience with Pirquet's method, and that the reason certain diseases or some physiological conditions, for example, menstruation and pregnancy, have been thought to depress sensitivity to tuberculin rests on the use of an insufficiently sensitive technique. This means, doubtless, that the depression of sensitivity is a relative matter.

The two of the 4 cases of measles where depression of the tuberculin reaction was noted may be explained by the fact that these children already were only faintly positive before measles; this fact may well have caused negative results. The other two negatives remain unexplained, although with higher concentrations of tuberculin the results might have been different. The children with chickenpox showed no change in their reactivity to tuberculin. As for the variation in the degree of reactions in the group with mumps, we have no explanation to offer.

CONCLUSIONS

1. A group of 118 children convalescing from tuberculosis who developed acute contagious diseases was studied.

2. No definite evidence was found to support the prevalent belief that measles, chickenpox, whooping-cough, mumps, scarlet fever and diphtheria have a deleterious effect on tuberculous lesions in the lungs of children.

3. No definite evidence was found to support the belief that the above diseases depress allergy to tuberculin in a child with healed or active tuberculosis.

4. Further data were discovered to strengthen the contention that exacerbations or remissions are fairly common occurrences during the course of childhood-type tuberculosis, and that they may occur in the presence or absence of intercurrent contagious diseases.

STREPTOCOCCUS THROAT INFECTIONS IN TUBERCULOUS CHILDREN[1]

GERTRUDE F. MITCHELL

This paper presents a report of an epidemic of sore throat which occurred in the children's division of the Maybury Sanatorium. This study was undertaken, first, because of our own curiosity as to the consequences of such an infection and, second, because of the paucity of material in the literature on this subject.

Just when the epidemic began is difficult to say for it was upon us before we realized with what we were dealing. The first cases in which we have complete data occurred early in December, 1935. The last case reported had its onset on April 27, 1936. Quite a large number of cases occurred during the last week in December and the first week in January. A slight peak appeared again during the latter part of January and early February. On the whole, however, the cases were fairly well distributed over a four-month period.

Nearly all of the children in the unit have childhood-type tuberculosis. Of 121 children, 89, or 73.5 per cent, were affected. Twenty-one children had two attacks of sore throat and 4 children had three. Eighteen of the 42 employees in this division are known to have been ill during this period, many of them with the same symptoms and clinical picture observed in the children. There may have been others who did not report their illness, as some did not come for medical advice until they had been sick for nearly a week.

The usual contagious disease precautions were observed. The children were isolated as soon as they had a complaint or had an elevated temperature. Unfortunately, new cases occurred so rapidly and continuously that it was necessary to move many children back to the wards after their temperatures had returned to normal, but before their throats appeared normal. An intensive study was made of the milk supply, but the examinations showed nothing which would lead us to believe that the milk was the source of the infection (1, 2, 3). There-

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

fore, we were of the opinion that the high incidence was due to exposure before isolation occurred and to the early returns to the wards (4, 5). Many of the children attended school in the Sanatorium. School was discontinued for ten days in January, and visitors were excluded from rooms and wards, but no striking results could be seen as a result of these procedures.

Usually the attack began with a sudden elevation in temperature of 102° to 105°F., accompanied by sore throat and headache and often some abdominal pain. Examination revealed redness of the throat and tonsils which frequently were swollen and covered with grayish patches of membrane. Sometimes the uvula was red and oedematous. The tongue suggested the scarlet fever tongue in appearance and not infrequently the buccal mucosa was very red. The cervical lymph nodes were enlarged and sometimes tender. Usually there was only a slight nasal discharge. At the beginning of the epidemic, the smaller children, almost without exception, had very red tympanic membranes, the redness even extending a short distance down the wall of the external canal. Early in the epidemic many tympanic membranes were opened; in some, a small amount of thin, purulent material was present, in others no pus was obtained. As a rule convalescence was prompt at all ages. The temperature returned to normal on the third or fourth day, and the symptoms subsided usually one to two days after the drop in temperature. However, the throat was rather slow to heal and a moderate degree of cervical adenitis was persistent in a large number of cases. Boys and girls suffered equally. The younger children were the first attacked and had more complications than the older ones. This was especially true of the group under four years of age.

Laboratory studies revealed facts of interest. Out of a total of 91 throat cultures, 78 contained *Streptococcus*; 20 showed *Streptococcus anhaemolyticus*; 53 showed *Streptococcus haemolyticus* or *viridans* or both; and 5 showed *Streptococcus anhaemolyticus* with some haemolytic forms. In 87 cases (separate attacks) in which cultures were made, 77 showed *Streptococcus*. These data are shown in table 1. The haemolytic streptococcus was the predominant microörganism in 40 cases, *Micrococcus catarrhalis* in 5 cases, haemolytic staphylococcus in 5 cases, and nonhaemolytic staphylococcus in 6 cases. In many cultures a haemolytic staphylococcus was present either alone or with a haemolytic streptococcus. *Micrococcus catarrhalis* was present in a large number of cultures (40). When this microörganism was predominant, the throat

symptoms were mild but persistent, the generalized symptoms were more marked and were present over a fairly long period of time, and the fever was lower than in the average case where the haemolytic strepto-

TABLE 1

FORM	NUMBER OF CASES
Streptococcus haemolyticus	33
Streptococcus viridans	7
Streptococcus anhaemolyticus	18
Streptococcus haemolyticus and viridans	13
Streptococcus haemolyticus and anhaemolyticus	4
Streptococcus viridans and anhaemolyticus	1
Streptococcus viridans, haemolyticus and anhaemolyticus	1

TABLE 2

COMPLICATION	NUMBER OF CASES	PERCENTAGE OF INCIDENCE	PERCENTAGE OF INCIDENCE IN LITERATURE*
Otitis media			
Suppurative	16	15.5	
Nonsuppurative	8	8.9	
Total	24	26.9	3.0
Mastoiditis			
Suppurative	1		1.6
Nonsuppurative	1	2.2	
Pneumonia	5	5.6	1.6
Bronchitis	4	4.4	
Peritonsillar abscess	1	1.1	2.5
Cervical adenitis			
Suppurative	1	1.1	4.6
Nonsuppurative	4		
Conjunctivitis and blepharitis		4.4	2.0
Rash	4	4.4	4.0
Wry neck	2	2.2	
Stomatitis (Vincent's)	2	2.2	1.0
Pyelitis	1	1.1	
Vaginitis	1	1.1	
Increase in tuberculous lesion	14	15.7	

* Capps, J. A.: Streptococcus sore throat, Nelson Medicine, *2*, p. 24.

coccus was predominant. These patients presented the clinical picture usually associated with influenza. Toward the end of the epidemic, *Streptococcus viridans* was encountered with increasing frequency and many different microörganisms were present in a given culture.

Treatment was symptomatic. No sera were given. At first nearly all throats were painted with an alcoholic solution of mercurochrome. This was discontinued upon the recommendation of our nose and throat consultant. Our impression was that recovery was more rapid when this more or less traumatic treatment was stopped.

Complications were numerous and disturbing, but the incidence was no higher than that usually reported in similar epidemics, except the ear infections and chest complications (1, 5, 6). They are shown in table 2. Eleven of the 16 cases of suppurative otitis media had almost pure cul-

TABLE 3

COMPLICATION	STREP. HAEMOLYT.	STAPH. ALBUS	STAPH. HAEMOLYT.	STREP. OR M. CATARRH.	STREP. ANHAEMOLYT.	NO CULTURE	TOTAL
Number of children	19	3	1	1	4	8	35
Suppurative otitis media	11	1	1		1	2	16
Nonsuppurative otitis media	1	2				3	6
Cervical adenitis	1	1	1		1	1	5
Bronchopneumonia	1	1		1	1	1	5
Bronchitis	2		1		1		4
Rash	4				1		5
Stiff Neck	2						2
Mastoiditis	1	1					2
Quinsy	1						1
Pyelitis	1						1
Stomatitis	2					1	3
Conjunctivitis	1				1	1	3
Blepharitis		1					1
Vaginitis	1						1
Total	29	7	3	1	6	9	55

tures of haemolytic streptococci. Complications in relation to the causative microörganisms are shown in table 3.

Roentgenograms of the chests of all the children affected were made after their acute symptoms had subsided and their throats appeared normal. Whenever necessary more than one roentgenogram was obtained to rule out nontuberculous processes in the lungs. Fourteen children showed an increase in their pulmonary disease. Twelve children who were ill during this period were not included in the group reported because of incomplete diagnosis; 4 of these had some increase in

their tuberculosis. If, perchance, they belong in this group the number with reactivation of their pulmonary disease is eighteen, or 14.8 per cent of all the children in the hospital. Of the 89 children included in this study, 15.7 per cent had an increase in their tuberculosis. None of the children who escaped this acute illness showed any increase in their

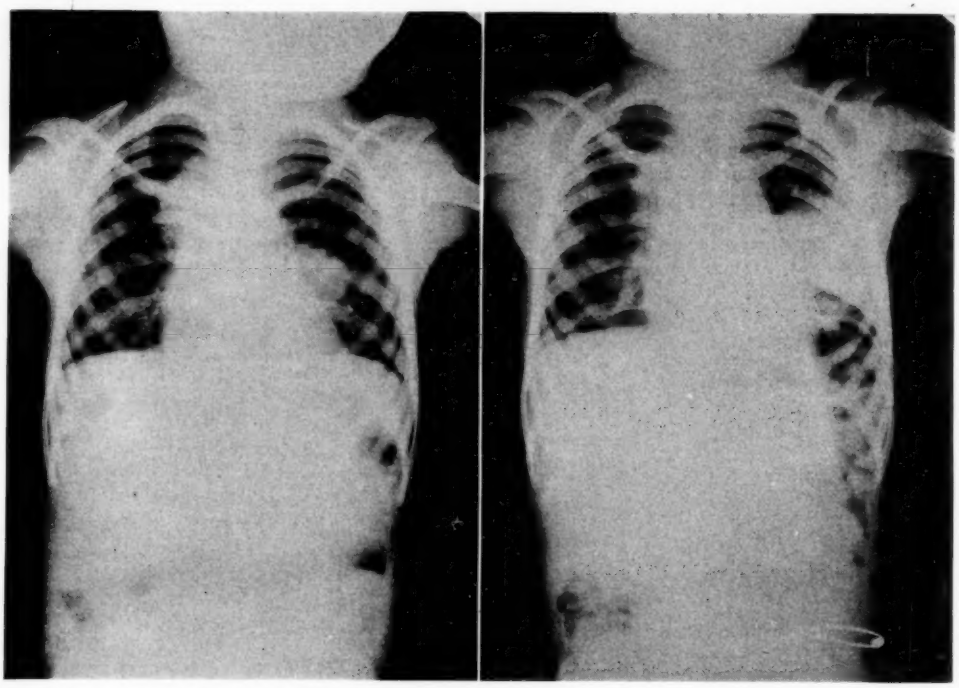

FIG. 1 FIG. 2

FIG. 1. E. R., March 3, 1936, before acute throat infection. Tuberculosis involving the tracheobronchial lymph nodes which showed only slight improvement on the right during the previous six months. Child entirely asymptomatic until onset of throat infection which occurred nine days after this routine X-ray film was taken.

FIG. 2. Same patient, March 18, 1936, eight days after onset of acute throat infection showing extensive infiltration in the left lung adjacent to known tuberculous involvement of the lymph nodes. Parenchymal disease cleared completely in eight months.

disease. Among those whose tuberculosis became worse no deaths occurred, and about half had only a temporary clinical setback.

Thus, 14 of 89 children experienced definite exacerbations. In 6 of these the disease appeared in parenchyma previously involved. An increase in the degree of tracheobronchial lymph node enlargement and also new parenchymal disease occurred in two children. New paren-

chymal lesions appeared in 5 cases, the disease developing in the contralateral lung in one case (figures 1 & 2). One child developed pleurisy with effusion. There were no cases of meningitis, peritonitis, enteritis or renal tuberculosis (table 4).

The tuberculous lesion cleared completely within six months in 5 cases and cleared completely within a year in 3 cases. Five children are still in the Sanatorium; 4 of these have shown some improvement and one is unimproved. The course of one is not known (table 5).

TABLE 4

Character of tuberculous exacerbations

Increase in parenchyma previously involved		6
Increase in tracheobronchial lymph nodes and new parenchymal infiltration		2
New parenchymal disease	On same side as tracheobronchial enlargement	4
	In contralateral lung	1
Pleurisy		1
Total		14

TABLE 5

Fate of lesions (old and new) in children with exacerbations

Cleared in 2 months	1
Entirely cleared in 6 months	4
Entirely cleared in 12 months	3
Improved (still in the Sanatorium)	4
Unimproved	1
Course not known	1
Total	14

The following case is presented as illustrative of the course of many of the children with exacerbations.

E. R., a four year old colored girl, was admitted to the Sanatorium on September 22, 1935 with a history of four attacks of fever, cough, abdominal pain, anorexia and loss of weight, each attack lasting about three weeks. The X-ray showed bilateral enlargement of the tracheobronchial lymph nodes. One month after admission her temperature, pulse and respiration became normal and remained so until the onset of her acute throat infection. She was without symptoms except for cough. No marked change was noted in her pulmonary disease until March 3, 1936 (figure 1) when a slight decrease in the lymph node enlargement was reported. On March 12, 1936 she had fever

and complained of sore throat. A diagnosis of acute tonsillitis was made. No new chest findings were noted. Three days later the chest findings were suggestive of bronchitis. There were no signs of consolidation. On March 18, 1936, examination revealed signs of consolidation and an X-ray film was obtained which showed extensive parenchymal infiltration in the middle and basal portions of the left lung. Another roentgenogram taken thirteen days later showed a slight decrease in density of the area of consolidation, but an increase in the extent of the infiltrations. Eight months later no parenchymal disease was visible in the roentgenogram, but the lymph node enlargement was still present.

The record of all the children in the unit during the same season of the previous year was reviewed. One of the wards at that time had a somewhat similar "epidemic" of sore throat, 17 children being affected at that time, and one of this group developed scarlet fever. Six of 106

TABLE 6

Results of Dick tests

DATE TESTED		NUMBER POSITIVE	NUMBER NEGATIVE
2/12/36	Those having the infection	38	38
	Those not having the infection	20	22
8/16/36	(Only sick children Dick tested)		
	Those having the infection	50	37

children, or 5.6 per cent, showed progression in their pulmonary disease during this period. On analysis it is found that 3 of the 6 had quite severe sore throats, the tuberculosis in one had been progressing before this period, and one had possibly nontuberculous pneumonia.

In various reports attention has been called to the effect of acute infections on tuberculosis with especial emphasis on measles and pertussis. Wollenstein and Spence (7) stated that, in comparing tuberculous and nontuberculous groups with respiratory infections, there is an increase in the number of tuberculous patients as respiratory infections subside, due to the fact that general resistance is diminished, which allows latent tuberculous foci to become active. Mitchell and Griffith (8), Knopf (9) and others supported the contention that lowered resistance, especially following respiratory infections, is an important predisposing factor.

Nalbant (10) reviewed 147 attacks of acute contagious disease (measles, scarlet fever, mumps, pertussis) occurring in 118 children in this Sana-

torium and was unable to find that there was any appreciable effect on the course of the tuberculous disease or on the eventual outcome. Hershey and Ward (11) came to the same conclusion regarding the effect of pertussis on children with tracheobronchial tuberculosis. Antoniazzi (12), studying the effect of simultaneous tuberculous and streptococcic infection, concluded that tuberculous lesions, and in particular those of the lungs, do not show any definite change, qualitative or quantitative, during a streptococcic focal infection. The findings presented in this paper do not warrant this conclusion nor do they justify the assumption that the course of the disease is unaffected by acute upper respiratory infection. In a study of tuberculosis in childhood at the Maybury Sanatorium, Nalbant (13) found that 14 per cent of all the children in the institution showed reactivation of their tuberculosis at some time during the entire period of hospitalization. Our group of cases in the same hospital had 14.8 per cent showing an increase in their disease within a period of only four months.

Dick tests were done on February 12, 1936 and August 16, 1936. The results are given in table 6. In the later tests we found that there was a slight increase in the number of positive reactors.

CONCLUSIONS

1. An epidemic of streptococcus sore throat occurring in tuberculous children is reported.
2. The course was much the same as that reported by others in groups of nontuberculous children.
3. The younger children were more severely affected and had more complications.
4. There was an unusually high incidence of otitis media.
5. A greater incidence of pneumonia is reported than is usually found in nontuberculous children.
6. There was a slight increase in the number of positive reactors to the Dick test after the throat infection.
7. The number of children showing roentgenographic evidence of increase in their tuberculous infection is definitely greater than is usually experienced in the course of routine check-ups in an equal number of children during a period of four months.

Acknowledgment is made of the valuable assistance of Dr. Edna M. Jones in assembling the data for this paper.

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TUBERCULOSIS WORK AMONG NEGROES IN PHILADELPHIA[1]

With Special Reference to the Negro Bureau

HARVEY DEE BROWN[2]

The Negro population of Philadelphia has increased steadily since 1900. Each census decade has brought a large number of colored people into the community to be assimilated by its industrial, social and health life.

In 1900 there were 63,000 Negroes in Philadelphia. Ten years later nearly 25,000 had been added to this number. In 1920 the number had increased to 134,000 and in 1930 there were 220,000 Negroes in the city.

In 1910 the reported death rate from tuberculosis among Negroes stood at the high point of 608 per 100,000. At that time Negroes shared in the general health activities of the city, and were welcomed by such special agencies as existed, but no successful method of reaching this large part of the population had been found. It was evident however that, both for their own sake and for that of the community as a whole, exceptional efforts should be put forth to help them in their fight against tuberculosis. Often handicapped by personal immaturity they were strangers in a strange environment whose worst features fell to their lot in terms of bad housing, low wages, heavy work and exploitation.

The tuberculosis death rate among Negroes has been three to four times as high as that among the white population since 1910. While at present in Philadelphia they constitute 11 per cent of the population, they provide 38 per cent of the deaths from tuberculosis. But the Negro tuberculosis death rate has declined since 1910 almost as continuously as that of the whites. The percentage of decline has not been quite as great but it has been nearly so. Thus the white death rate in 1920 was 119 and in 1935, 44, a decrease of 75 points or 63 per cent of the 1920 rate. The Negro rate on the other hand was 362 in 1920 and in 1935, 174, a decrease of 188 points or 52 per cent of the 1920 rate.

Soon after the results of the 1910 Census became available special efforts to combat tuberculosis among Negroes began in Philadelphia. These

[1] From the Philadelphia Health Council and Tuberculosis Committee, Philadelphia, Pennsylvania.

[2] Deceased.

efforts combined a sympathetic recognition of racial kinships by the use of Negro workers, a continued coöperation of several agencies and the use among Negroes of the scientific procedures applicable to the whites in combating tuberculosis. This paper endeavors to sketch the history of the development of this work among Negroes and the principles involved both in the early efforts and in the developments which have followed.

EARLY WORK AMONG NEGROES 1914–1921

The first efforts to combat tuberculosis among Negroes in Philadelphia were those of the Henry Phipps Institute which was opened in 1903 for the study, treatment and prevention of tuberculosis. During its early years the Institute found it difficult to do satisfactory work with Negro patients although it was located in the "black belt," a section of the city which had many colored residents. Negro patients who came to the dispensary more or less by accident could seldom be induced to be regular in their attendance and but little progress was made in aiding them. Educational work which served to bring increasing numbers of white patients did not reach the Negroes or advance perceptibly their interest in examinations for tuberculosis and medical care. Less than 100 Negroes were cared for annually during the first ten years of the life of the Institute.

Dr. H. R. M. Landis, Director of the Clinic and Sociological Departments of the Institute, was much concerned with this failure to reach Negroes in large numbers in view of the extensive prevalence of tuberculosis among them. He conceived the idea of having Negro nurses and later Negro physicians work with this section of the population. He was convinced that knowledge of their own race and sympathetic understanding of their people's point of view would aid in arousing interest and attract Negroes to the services which the Institute offered. A Negro nurse was therefore assigned to work among her own people in February, 1914, and later two additional nurses were employed.

There was at first no carefully thought out plan for the nurse's work. Doctor Landis relates that when the first nurse appeared he hardly knew what to tell her to do. "One nurse and some 80,000 Negroes to tackle! For about a half hour we fenced, she trying to find out what I wanted of her, I racking my brain to tell her. As I sat looking out of the window a Negro woman came out of one of the houses directly opposite the Insti-

tute. That did the trick. I said, 'Go over to that house, tell them who you are and what you are here for. Make it a friendly visit. Then start west on Lombard Street ringing door bells and tell them your story. Be here at the Institute in the morning to receive any clients you may have uncovered in the afternoon. Keep it up day after day.' Owing to the grapevine communication these people have she soon became known and looked for. Later she began talking in the churches. That's what happened! The same tactics were used in organizing other clinics. For every case the nurse sends in, five or six come on the advice of a friend. While the nurse sees relatively few the information spreads from one to the other and in this way reaches large numbers."

The results of the nurse's work became evident almost at once in a new attitude on the part of Negroes and in an increased and more regular attendance at the dispensary. At the beginning of 1915 a Negro physician was employed and shortly thereafter a special Negro clinic was opened at the Institute. Thus began a systematic campaign against tuberculosis among Negroes in Philadelphia which enlisted the interest of other agencies and which with modifications and expansions has continued for 23 years.

The aims of this early work were eventually defined as follows: (*1*) to develop a sense of responsibility among Negro people for their health, (*2*) to carry health educational activities to Negro residents, and (*3*) to stimulate the development of dispensary work for this part of the population. If we add two further purposes (*4*) that of securing hospital care and modern treatment for Negroes, and (*5*) the training of Negro physicians and nurses, this early formulation might still describe the aims of this service.

During the years following 1915 the staff of Negro physicians and Negro nurses was increased. Negro clinics were maintained at the Institute for all ages and in 1918 the Chest Department of the Jefferson Hospital opened a clinic. Negro patients were also referred to the state clinics in Philadelphia. Each month of those years told the story of a large number of persons examined at the clinics, a steady stream of patients sent to hospitals and sanatoria, and a substantial amount of public health nursing work in Negro families.

In 1916 a demonstration of the work of a Negro nurse was begun in the Visiting Nurse Society of Philadelphia. After two years the value of this work has been so thoroughly shown that the Society employed two

Negro nurses and later increased this nursing staff to five. Since that time several Negro nurses have been continuously engaged in the work of that Society.

An important feature of this early work was the health education of Negroes. This objective has always been present. An Advisory Committee composed of Negro physicians and laymen was formed in 1918, which had an extensive roster of subcommittees assigned to different phases of educational work. District health councils of Negroes for educational efforts were formed in 22 localities. Classes for the health instruction of mothers were conducted. Ministers were asked to talk about tuberculosis to their congregations or to yield their pulpits on occasion to Negro nurses. Special leaflets were prepared and distributed in large numbers. Contacts were made with the increasing number of Negro organizations of various kinds and their aid enlisted. Insurance companies serving Negroes were stimulated by special institutes to become the bearers of health information to their policyholders. Negro doctors and nurses worked overtime meeting appointments for educational talks.

Out-of-door demonstrations with motion pictures and music by bands drew large crowds. A special demonstration of this kind appears to have been of an experimental character so detailed is the report of its preparation and program. It relates that a house-to-house canvass was made and that 6,500 Negroes crowded the school playgrounds for a varied program of talks, motion pictures and music. Special educational work was done at the Round Table, a Negro group. In a congested centre of Negro population a registration office was opened where literature was distributed and information given regarding examinations and hundreds of problems of homekeeping in health and in sickness. The Modern Health Crusade was introduced into Negro public and parochial schools. Following this, nutrition classes were organized at which mothers were instructed in nutrition, diet for children and the importance of having physical defects corrected, this work being done by Negro physicians and nurses with the supervision of the staff of the Phipps Institute.

Confidence in mass education was stronger in the decade 1910–1920 than in the one which followed it. If lip service was still paid to the idea, efforts tended steadily to focus themselves upon conferences with individuals and smaller groups. It is almost impossible now to return to the enthusiasm which characterized the mass efforts of earlier years. There can be no doubt, however, but that the widespread education of

the Negro population which preceded the early twenties prepared the way in Philadelphia for the developments of later years in tuberculosis work.

THE NEGRO BUREAU 1922–1936

A number of agencies coöperated in this early work among Negroes. The Whittier Centre, an organization active in Negro affairs, which initiated a number of movements of social welfare for this race, was one of them. This organization paid the salary of the first Negro nurse in 1914. The Pennsylvania Tuberculosis Society by its Philadelphia Committee participated in these efforts, and when in place of that Committee the Philadelphia Health Council and Tuberculosis Committee was organized in 1919, it placed Negro work as one of its main activities. The Mercy Hospital, an excellent Negro institution, coöperated continuously from the first. The Chest Department of the Jefferson Hospital maintained a Negro dispensary and the Henry Phipps Institute carried the major part of clinic work, direction, teaching and white supervision for the Negro staff.

The activities of these various agencies working for Negroes were brought together in the early twenties under the designation of the Negro Bureau which has continued and developed this work. Its formal beginning was by appointment of the Philadelphia Health Council and Tuberculosis Committee.

The Negro Bureau began under the direction of Dr. H. R. M. Landis, of the Henry Phipps Institute, and Dr. Elmer H. Funk, the Director at that time of the Chest Department of the Jefferson Hospital. It received support and active coöperation from all of the agencies mentioned and their agreement upon a definite statement of the aims of the work. Until his death in May, 1932, Doctor Funk was associated with Doctor Landis in the direction of the Bureau. Since that time Doctor Landis, aided by the medical and nursing staff of the Institute, has directed the Bureau work. The Director of the Philadelphia Health Council is Secretary of the Bureau, having charge of the Health Council's contribution to the work and of the records of the few meetings other than medical and technical which are still necessary.

The first report of the Negro Bureau by Doctor Landis and Doctor Funk dated June 1, 1922, states clearly the aims of the Bureau thus:

> It may be proper to point out at once that the work of the Negro Bureau is in its inception a part of a program already appreciably advanced, the immediate purpose of which is to reduce the death rate from tuberculosis among the

Negroes of this city to the level of that prevailing among the whites of the same social and economic standing, and to so arrange that any further increment of health may accrue to white and colored alike. . . .

Anti-tuberculosis work among Negroes in Philadelphia has passed through the purely experimental stage and can be considered to have established certain facts. It is clear that the methods which have been developed for this work among the white population can be successfully applied to the colored. To this there appears to be but one limitation; namely, the detailed work in the clinics and in the field must be very largely done by colored physicians and nurses who must at the same time have constant association with and supervision by sympathetic whites.

It is our belief that this method is essentially that of any successful past effort dealing fundamentally with the great racial problem as our country has faced it since the abolition of slavery; namely, the Negro to do for himself with the most sympathetic and expert advice and guidance by his white fellow citizens. If this be accepted as a true thought then perhaps the most serious question which could be raised against the durable success of this venture is accounted for already. We need anticipate no failure on the part of the colored to do their part; it is our problem to so arrange matters that we may be reasonably assured that we can continue to do ours.

The report also pointed out that the Henry Phipps Institute began the work among Negroes and had been able to conduct it to its condition at that time only by reason of the essential help continually given by other persons and organizations. It indicated the importance of having the Phipps Institute continue to be the centre of this activity, particularly as it stood as such in the eyes of those Negroes who had at that time or who had previously had an important connection with the Institute. This relationship, it was believed, should be maintained until there had been thought out and agreed to by all concerned some well defined plan for a transfer of responsibility. This policy was adopted and has been consistently followed.

Prior to the formation of the Bureau, work had been done largely in the southern section of the city but it was felt that it should be extended to other localities having a large Negro population. The need for further knowledge of the settlement of Negroes in the city was felt and a study of the Negro tuberculosis problem in Philadelphia was therefore undertaken by the Whittier Centre with the aid of the other agencies in the Bureau (1). The Centre also made a survey later of the health of Negro babies born in 1922 in four wards in Philadelphia, this having been suggested by the findings of the study of the tuberculosis prob-

lem (2). A number of other minor surveys in various localities were made.

The facilities for Negro work soon increased under Bureau direction. The dispensaries at the Phipps Institute and at the Jefferson Chest Department were supplemented by the opening in the heart of a Negro concentration in North Philadelphia of Health Clinic Number 3 in 1923, and two years later Health Clinic Number 4 was opened in the Negro district in Germantown. The latter was for seven years especially successful in reaching children, and in intensive educational work with families. Reduced funds because of the depression led to its discontinuance in 1933, the tuberculosis patients being transferred to the City Chest Clinic at the Germantown Hospital.

Health Clinic Number 3 in North Philadelphia made steady progress from the beginning and has an enviable record of 13 years of work. As the dispensary developed there were organized prenatal, preschool, school and adult clinics as well as a nose and throat clinic. The laboratory work has been done at the Phipps Institute. Tuberculin testing was introduced for all patients in 1932. The coöperation of physicians in the district covered by the clinic steadily increased as shown by the number of patients referred for diagnosis. A few years ago an arrangement was made with the City Division of Tuberculosis by which all cases reported from the district to the Division, and all tuberculosis deaths occurring there, are referred to this clinic, which does the medical and nursing work in connection with them.

The Jefferson Chest Clinic after several years of pioneer work ceased to be a Negro Bureau agency in 1930, although it continued service for Negroes with Negro physicians. The Whittier Centre, after becoming a member of the Welfare Federation, was granted two nurses who were assigned by the Centre to work under Negro Bureau supervision, but later this agency became inactive in health work.

Notwithstanding these changes the work of the Bureau steadily increased and developed. The Bureau nurses not only served in the clinics but also provided systematic home supervision to more than 500 homes annually where tuberculosis existed. A regimen of diet and care was instituted and the prevention of the communication of the disease was sought. The nurses of the Negro Bureau have all been for several years members of the National Organization for Public Health Nursing, meeting the same standards as white nurses.

A systematic plan for the training of student nurses has also been

carried out in coöperation with the Mercy Hospital, which maintains a training school for nurses. Two months' intensive training is given under Bureau direction to six nurses each year. They work under a Negro Field Supervisor appointed in 1929 who is responsible to white direction. To this field experience is added a series of eight lectures and two demonstrations given at the Mercy Hospital to these nurses. Other senior nurses are sent by this institution to the Visiting Nurse Society of Philadelphia that they may gain that type of experience. All new students entering this school of nursing are examined at the Phipps Institute with tuberculin tests and X-ray examinations upon entrance and afterwards at yearly or other intervals while in training and immediately before leaving the school after graduation. A scholarship is provided by the Philadelphia Health Council whereby graduate nurses of the Mercy Hospital are able to take postgraduate training after finishing their term of service with the Bureau. Because of the need for competent Negro nurses a number have been called to other fields before their postgraduate work.

The work of the physicians of the Bureau is in immediate charge of a Negro supervisor who is responsible to white direction. There is also a Chief of Clinics, who is a Negro. All Bureau physicians, nurses and student nurses participate in the therapeutic and pathological conferences at the Phipps Institute with the white physicians of the Institute staff and with other Negroes who come from outside the city for special training at the Institute. At these conferences certain selected cases are studied. The social situation, including living conditions, number of persons in the household, family income, rent paid and attitudes of the family are reported by the nurse. The physician's findings in physical examination, sedimentation test, Wassermann reaction if indicated, tuberculin test, X-ray examination, urine and sputum examinations and blood-pressure are presented. The X-ray films are exhibited and ordinarily the patient himself appears before the group. On the basis of these presentations consideration is given by the entire group to the methods to be followed in handling the patient.

There are usually a number of Negro physicians in training at the Institute. These have been sent by such agencies as the Rosenwald Fund, the Rockefeller Foundation and the Department of Health of Washington, D. C. The latter has also sent Negro nurses for training. All of the internes at the Mercy Hospital come to the Institute for a six weeks' period of instruction.

The patients of the Negro Bureau, as may be seen, have the benefit of all accepted diagnostic measures. Those with tuberculosis are referred to the city or state sanatoria for treatment, excepting those recommended for collapse therapy. This is initiated at the Mercy Hospital or other institutions and continued at the Institute, which has maintained a large pneumothorax clinic for several years. Those patients who remain in their homes receive systematic nursing supervision. Those referred by physicians from the district of Health Clinic Number 3 receive the same attention as other patients and reports are sent to the private physician.

The educational work of the Bureau has advanced from the mass education of earlier days to more intensive instruction adapted to individual situations. The training of Negro physicians and nurses, and through them the education of patients and families, has for the most part taken the place of mass demonstrations.

One effort, however, of group character in health education and fund raising may be mentioned. In 1927 the Bureau undertook popular activities among Negroes by a special educational worker of that race. This took the form of organizing Negro Health Clubs. A plan was devised of installment payments of ten cents a month, each payment being punched on a membership card. Those who paid as much as $1 were enrolled as full members and sent a sheet of Christmas Seals without cost in December. This was an attempt to stimulate responsibility for health work among Negro people and to secure funds for the salary of one nurse. During the two years in which this work was carried on, 1,411 members were enrolled in Negro Clubs whose contributions and dues amounted to $1,558. The plan failed in securing adequate funds but afforded an opportunity for group education which stimulated attendance at the clinics. Educational talks given in connection with this work numbered 245, with an attendance of 23,519 persons. Before this effort and following it, the normal educational work of the Philadelphia Health Council of health talks and the showing of films extended to various Negro and mixed groups. In 1936, 48 programs of this kind were given with 33 talks and the showing of 90 films to an attendance of 5,562. Other recent years have similar records including coöperation with Negro doctors, settlement groups, the Armstrong Association, a Negro welfare body and Negro Health-Week meetings.

At the present time two municipal chest clinics and a clinic at Douglass Hospital have Negro physicians and nurses. Nearly every clinic in the

city, however, has some Negro patients, 5,242 having been served in 1936. Sixty per cent of these were served by the Negro Bureau whose work constituted 19 per cent of the total tuberculosis clinic work of the city.

Under the supervision of the Negro Bureau is also a clinic with Negro physicians and nurses established in 1930 in the neighboring city of Chester, Pennsylvania. This has been supported by the Pennsylvania Tuberculosis Society and the local Tuberculosis Association. It has a strong Negro Committee which sponsors it and aids financially. After three years a part of its maintenance was assumed by the State Department of Health. The clinic serves about 1,000 patients a year, following the methods and the record system used by the Negro Bureau.

For a number of years the household has been considered by the Phipps Institute as the unit in tuberculosis work and this principle is maintained in the Negro Bureau work. Records of every family in which there is tuberculosis are kept in a family folder which contains the medical record of the patient, the family record, the nurses' reports and laboratory reports. Patients with positive sputum are designated by a star as a source of danger and as needing special nursing attention.

At the present time there are the following Negro workers on the staff of the Bureau: a Supervisor, Clinic Chief and eight physicians giving part time to this work; a Field Supervisor of nurses, seven nurses and one student nurse. Two large Bureau clinics are in operation, one at the Phipps Institute and the other in the northern part of the city.

The number of patients served by the Bureau clinics reached over 2,500 in 1926, and beginning with 1931 there have been from 3,000 to 3,500 each year. Few expansions have been made during these last years because funds were not available and an increasing amount of Negro work is being done by municipal clinics. The last report of the Bureau, that for 1936, is typical. It gives the following items: total patients 3,140, new patients 1,386, diagnosed tuberculosis patients 536, visits made to clinics 13,137, home and agency visits made by nurses 4,244, services to individuals 13,490, and physicians' clinic hours 3,346.

Special examinations were made as follows: tuberculin tests 1,989, X-ray examinations 1,245, sputum examinations 1,888, and Kahn tests for syphilis 1,313. There were 112 patients who began collapse treatment at the Mercy Hospital. A total of 3,865 pneumothorax treatments were given at the Phipps Institute.

The cost of the Negro Bureau work for several years has been about $35,000 per year, which is divided between the Henry Phipps Institute

and the Philadelphia Health Council and Tuberculosis Committee in the approximate ratio of three-sevenths by the Phipps Institute and four-sevenths by the Health Council. During the 23 years since 1914 the amount of Christmas seal funds devoted to this Negro work has been $351,518. The expenditures of the Mercy Hospital and of the city for Negro services carried on in accordance with the principles of the Bureau undoubtedly bring the amount now spent for this type of Negro work in Philadelphia to $50,000 per year.

FUTURE DEVELOPMENT

What is to be the future of this work? Its immediate goal is, as stated, "to reduce the death rate from tuberculosis among the Negroes of the city to the level of that prevailing among the whites with the same social and economic standing." The 1922 report which defined this purpose mentioned another goal, thus: "It is recognized by all that certain aspects of this work are the proper function of the municipal or state health departments, and as the work develops it is intended to make every effort to have them participate and finally assume the routine operation of the dispensaries."

It also said, "It is clear that the extension of the work outside of the city, and even its full development here, must depend on the availability of adequately trained colored physicians and nurses in sufficient numbers. The Philadelphia work is admirably designed especially when further perfected and coördinated to serve as a training ground for these people."

Here then are two lines of development which reach into the future. The transfer of a part of the Negro Bureau clinic work to the official agencies of the city is a most desirable objective. The arrangement already made by the City Division of Tuberculosis with Health Clinic Number 3, whereby the normal tuberculosis clinic work among Negroes in that section of the city is done by this Bureau clinic, is a constructive preparation for the time when this work may be continued with present standards and effectiveness by the City Department of Public Health. Much remains to be done in the development of high standards in official health work so that trained and experienced Negro physicians and nurses will be recognized as essential to successful work among this race. But progress is being made in this direction. If ever the financial situation of the city makes possible expansion rather than curtailment of health activities, it may be confidently expected that the way will become clear to transfer a part of the Negro Bureau activities to the city.

It will probably, however, not be desirable that all of the Negro Bureau activities be so transferred. The need for encouraging high standards in Negro work, the correlation of the activities of different agencies and the training of Negro physicians and nurses by carefully supervised clinic and field experience, may make it desirable that a part of this work be retained indefinitely. While the value of Negro health workers for Negro people, especially of nurses, is pretty generally accepted both North and South, and the facilities for training them are increasing in the South, as is shown by the report of the Committee on Tuberculosis Among Negroes of the National Tuberculosis Association, these facilities are by no means adequate to provide all the personnel which is needed.

It would therefore appear that after a part of the Negro Bureau work has been transferred to city maintenance and administration as a demonstration which has been successfully completed, another part may be advantageously retained at the Phipps Institute to maintain the methods and standards found to be successful and to aid in the training of medical and nursing personnel needed for the difficult problems of tuberculosis among Negroes in our large cities.

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BACTERIOSCOPIC EXAMINATION OF STERILIZED SPUTUM

ELENA I. POLITOVA[1]

In order to avoid the possible dangers of infection with bacilliferous sputum, a method was developed to examine sputum specimens following sterilization.

The use of chemical substances for sterilizing the sputum is not satisfactory because it is not completely safe and because many of the minor microscopical details are altered by such substances.

In 1929 I published in the journal *Laboratory Practice* a preliminary note on the examination of sputum following sterilization in the autoclave or in a boiling water bath. The results obtained by this technique were satisfactory. In the meantime, the above data were verified on a larger material, a total of 260 sputum specimens.

It was first determined how long and to what temperature sputum had to be heated in order to render it sterile, while the morphological appearance and the tinctorial characteristics remained unaltered. It had to be determined that by such a procedure all morphological elements of the sputum, including tubercle bacilli and other microörganisms, remained unchanged and detectable by the usual methods.

The sputum jars are put into a water bath, in such a way that the water level does not reach above three-quarters of the height of the jar. The specimens are kept in boiling water for from 11 to 13 minutes. Samples of sputum treated in this manner were planted on egg medium following preliminary treatment according to Hohn's method. One such sample was injected into a guinea pig. Both cultures and guinea pig testified to the sterility of the specimens.

A total of 260 sputum specimens were examined both before and after sterilization. Of these, 235 yielded identical results. In 24 specimens elastic fibres were found only in the fresh and not in the sterilized portion of the sputum, while the opposite was true of one specimen. Curshmann spirals were found in five sterilized and in two fresh specimens. It was

[1] Moscow Regional Tuberculosis Institute, Moscow, U. S. S. R.

established that heart failure cells and other microbes are as easily demonstrable in sterilized as in fresh sputum. Gram stains of the sterilized sputum yielded clearer pictures than those of unsterilized specimens.

Charcot-Leyden crystals are, of course, destroyed by boiling.

SUMMARY

The bacterioscopic examination of sputum sterilized in a boiling water bath yields equally reliable results as that of unheated sputum. By preparing sputum in this way all possibilities of laboratory infection are eliminated.

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THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF THE NATIONAL TUBERCULOSIS ASSOCIATION

ABSTRACTS OF TUBERCULOSIS

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VOLUME XXXVI

JULY-DECEMBER, 1937

PUBLISHED MONTHLY

AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.

BY THE NATIONAL TUBERCULOSIS ASSOCIATION

THE

AMERICAN REVIEW OF TUBERCULOSIS
ABSTRACTS OF TUBERCULOSIS

VOLUME XXXVI AUGUST, 1937 ABST. NO. 1

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Total Pneumonectomy.—A detailed description of the technique of pneumonectomy for both right and left lung is presented. The method used is based upon a series of 10 total and 20 partial pneumonectomies. Of the 10 total pneumonectomies, 4 were on the right side and six on the left. Eight were operated upon for tumors of the lung and 2 for unilateral tuberculosis. In the group there was one death each due to diffuse lobular pneumonia, metastasis of the tumor to the brain, tuberculosis of the remaining lung, and pulmonary embolism.—*The Surgical Technic of Total Pneumonectomy, W. F. Rienhoff, Jr., Arch. Surg., February, 1936, xxxii, 218.*—(*L. F. B.*)

Contralateral Spontaneous Pneumothorax Complicating Lobectomy.—The author reports 3 cases, two of which died, of contralateral spontaneous pneumothorax occurring during lobectomy. Although no definite opening could be found at autopsy, it was concluded that a small opening was made through the mediastinum at the time of operation. Death in the third case was prevented, when it was found that the lungs did not expand well on discontinuing positive-pressure anaesthesia, by inserting a catheter between the ribs on the contralateral side, allowing the air to escape under water and continuing the positive-pressure anaesthesia. It is conceivable that contralateral pneumothorax might result from a rupture of one or several alveoli on the unoperated side if the patient's breathing is labored or too high positive pressure is delivered through the anaesthetic apparatus. Any change in the respiratory action, associated with failing of the pulse should immediately suggest contralateral pneumothorax. Increased positive pressure and an outlet for air on the contralateral side is the suggested procedure of choice.—*A Consideration of Contralateral Pneumothorax as a Complication of Intrathoracic Operations, H. B. Stephens, J. Thorac. Surg., June, 1936, v, 471.*—(*L. F. B.*)

Scaleniotomy.—The author employed scaleniotomy and phrenicoexairesis in those cases in which pneumothorax was tried with negative results, and plastic operation in some form or plombage was not indicated, or as a complementary operation in incomplete pneumothorax when plastic operation or cauterization could not be resorted to. The direct effect lay not simply in an increased collapse, but rather in a considerably reduced respiratory movement in that half of the thorax. Not much change in the shape of the thorax could be seen in a radiograph, but the decreased movement could easily be seen by direct illumination. Usually a marked improvement could be observed after the operation; cough, temperature and general condition were usually favorably affected. As a rule, expectoration increased